Report on the Deliberation Results

June 4, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Ongentys Tablets 25 mg
Non-proprietary Name	Opicapone (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	February 27, 2019

Results of Deliberation

In its meeting held on May 29, 2020, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, and the re-examination period is 8 years. The drug substance is classified as a poisonous drug, and the drug product is classified as a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

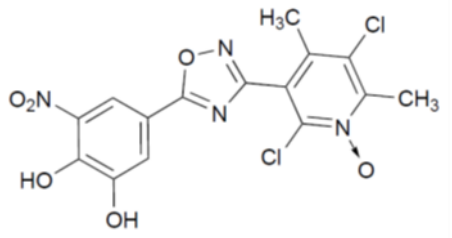
Review Report

May 12, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Ongentys Tablets 25 mg
Non-proprietary Name	Opicapone
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	February 27, 2019
Dosage Form/Strength	Tablets, each containing 25 mg of opicapone
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{15}H_{10}Cl_2N_4O_6$
Molecular weight: 413.17
Chemical name: 2,5-Dichloro-3-[5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl]-4,6-dimethylpyridine *N*-oxide

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the improvement of end-of-dose motor fluctuations (wearing-off phenomenon) in patients with Parkinson's disease when used in combination with levodopa/carbidopa or levodopa/benserazide hydrochloride, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The occurrence of symptoms including dyskinesia, hallucination, visual hallucination, and orthostatic hypotension should be further investigated.

Indication	Improvement of end-of-dose motor fluctuations (wearing-off phenomenon) in patients with Parkinson's disease by combination use with levodopa/carbidopa or levodopa/benserazide hydrochloride
Dosage and Administration	Opicapone is used in combination with levodopa/carbidopa or levodopa/benserazide hydrochloride. The usual adult dosage is 25 mg of opicapone administered orally once daily at least 1 hour before or after the administration of levodopa/carbidopa or levodopa/benserazide hydrochloride and at least 1 hour before or after a meal.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

September 19, 2019

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval	
Brand Name	Ongentys Tablets 25 mg
Non-proprietary Name	Opicapone
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	February 27, 2019
Dosage Form/Strength	Tablets, each containing 25 mg of opicapone
Proposed Indication	Improvement of end-of-dose motor fluctuations (wearing-off phenomenon) in patients with Parkinson's disease by combination use with a levodopa-containing formulation
Proposed Dosage and Administration	Opicapone is used in combination with a levodopa-containing formulation. The usual adult dosage is 25 mg of opicapone administered orally once daily at bedtime. Opicapone should be administered orally at least 1 hour before or after the administration of the levodopa-containing formulation.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Opicapone, originally developed by Portugal-based BIAL-Portela & C[a]., S.A., is a long-acting inhibitor of peripheral catechol-*O*-methyltransferase (COMT), a metabolizing enzyme for levodopa. The inhibition of COMT increases the bioavailability of levodopa so that levodopa in plasma is transported into the brain efficiently, and is thereby expected to improve end-of-dose motor fluctuations (wearing-off phenomenon) in patients with Parkinson's disease (PD). Entacapone, an approved COMT inhibitor in Japan, with its short duration to inhibit COMT, has to be administered in multiple doses per day along with the administration of levodopa/dopa-decarboxylase inhibitor (DCI) preparations. To address this issue, a once-daily drug, opicapone, was developed.

In Europe, opicapone was approved in 2016 as adjunctive therapy to levodopa/DCI combination formulations for adult patients with PD experiencing end-of-dose motor fluctuations which is not stabilized by the combination formulations. As of June 2019, opicapone has been approved in 32 countries and regions. In the US, an application was filed in April 2019, and is currently under review.

In Japan, the applicant began the development of opicapone in 20[redacted]. Recently, an application for marketing approval of opicapone has been filed based on results from clinical studies conducted in Japan and other countries, for the indication of "improvement of end-of-dose motor fluctuations (wearing-off phenomenon) in patients with Parkinson's disease by combination use with levodopa-containing formulations."

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a yellow powder. The description, solubility, dissociation constant, partition coefficient, hygroscopicity, intrinsic dissolution rate, melting point, and optical rotation were determined. While 6 crystal forms (A through F) were identified in the drug substance, Crystal Form A will be manufactured consistently on a commercial scale.

The chemical structure of the drug substance was elucidated by elemental analysis, ultraviolet-visible spectroscopy (UV/VIS), infrared absorption spectroscopy (IR), mass spectrometry (MS), ^{1}H-nuclear magnetic resonance spectroscopy (NMR), and ^{13}C-NMR.

2.1.2 Manufacturing process

The drug substance is synthesized by [redacted] using [redacted] and [redacted] as the starting materials.

[redacted] was defined as a critical step. [redacted] and [redacted], as well as [redacted] and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The drug substance specification includes strength, description, identification (IR, high performance liquid chromatography [HPLC], X-ray powder diffraction), purity testing (related substances, [redacted], and [redacted] by HPLC; residual solvents by gas chromatography [GC]), water content, residue on ignition, particle size, purity, and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows the main stability studies on the drug substance. The results of the photostability studies showed that the drug substance is photolabile.

Table 1. Main stability studies on the drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	3 production batches each	30°C	65%RH	Double-layered polyethylene bag + HDPE drum[a]	36 months [redacted] 24 months [redacted]
Accelerated		40°C	75%RH		6 months

a, light-shielding properties

Based on the above results, a retest period of 36 months was proposed for the drug substance when placed in a double-layered polyethylene (PE) bag and stored in a high density polyethylene (HDPE) drum at room temperature protected from the light according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E Guidelines. The long-term testing of the drug substance [redacted] will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet containing 25 mg of the drug substance.[1)] The drug product contains lactose hydrate, partially pregelatinized starch, sodium starch glycolate, magnesium stearate, hypromellose, titanium oxide, red ferric oxide, and Macrogol 6000 as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising [redacted], [redacted], [redacted], mixing, tableting, blending of film-coating ingredients, film-coating, and packaging/labeling (blister packs and bottles). The [redacted] step was defined as a critical step, and process control items and values were specified for the [redacted], [redacted], and [redacted] steps.

A quality by design (QbD) approach was used to address the following to establish a quality control strategy (Table 2).

- Identification of critical quality attributes (CQAs)

[1)] During the review process, the tablet was changed from scored to unscored tablets for medical safety reasons.

- Identification of critical process parameters (CPPs) based on quality risk assessment, design of experiments, and other factors.

Table 2. Outline of control strategies for the drug product

CQA	Control method
Appearance	Manufacturing process and specifications
Strength	Manufacturing process and specifications
Uniformity of dosage units	Specifications
Dissolution	Manufacturing process and specifications
Related substance	Manufacturing process and specifications

2.2.3 Control of drug product

The proposed specification for the drug product consists of strength, description, identification (UV/VIS, HPLC), purity testing (related substance [HPLC]), uniformity of dosage units (HPLC), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 3 shows the main stability studies on the drug product. The results of the photostability studies showed that the drug product is photostable.

Table 3. Main stability studies on the drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot batches	25°C	60%RH	Blister pack,[a] HDPE bottle[b]	24 months
Accelerated		40°C	75%RH		6 months

a, [redacted] film/aluminum
b, HDPE bottle + PE cushioning material + PP cap

Based on the above results, a shelf life of 36 months was proposed for the drug product in a blister pack ([redacted] film/aluminum) or in an HDPE bottle with PE cushioning material plus a polypropylene (PP) cap according to the ICH Q1E Guidelines. The long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Inhibition of human COMT (CTD 4.2.1.1-1)

Opicapone (30, 60, or 100 nmol/L) or vehicle (0.1% dimethyl sulfoxide [DMSO]) was added to a recombinant *E.coli*-producing human soluble-COMT (S-COMT) solution, to which adrenaline (1000 μmol/L) was added 0 to 180 minutes later for 10-minute incubation at 37°C. The amount of metanephrine formed was determined

by HPLC-electrochemical detection (ED). Opicapone inhibited S-COMT activity in a concentration-dependent manner, and S-COMT inhibition by opicapone did not differ greatly by pretreatment time.

Opicapone (50 μmol/L) was added to a recombinant *E.coli*-producing human S-COMT solution for 0 to 120 minute-incubation at 37°C. The product was determined by liquid chromatography-mass spectrometry (LC/MS). The results showed the formation of BIA 9-1100, the 3-*O*-methylated metabolite of opicapone, and BIA 9-1104, the 4-*O*-methylated metabolite of opicapone, which increased in a time-dependent manner.

Opicapone (60, 100, or 140 nmol/L) or vehicle (0.03% DMSO) was added to recombinant *E.coli*-producing human S-COMT solutions (5-40 μg/mL), to which adrenaline (1000 μmol/L) was added 5 minutes later for 10-minute incubation at 37°C The amount of metanephrine formed was determined by HPLC-ED, and an Ackermann-Potter plot was created. Opicapone exhibited tight-binding inhibition (*Nat Chem Biol.* 2015;11:416-23) against human S-COMT with an inhibition constant (K_i) of 0.02 nmol/L.

3.1.1.2 Inhibition of rat COMT (CTD 4.2.1.1-2)

Opicapone (75, 150, 225, or 300 nmol/L) or vehicle (0.03% DMSO) was added to a solution of S-COMT prepared from male rat liver, to which adrenaline (1000 μmol/L) was added 5 minutes later for 5 minute incubation at 37°C. The amount of metanephrine formed was determined by HPLC-ED, and an Ackermann-Potter plot was created. Opicapone exhibited tight-binding inhibition against rat S-COMT with a K_i of 0.2 nmol/L.

3.1.1.3 Inhibition of rat COMT by metabolites (CTD 4.2.1.1-2, 9)

Opicapone and opicapone metabolites, BIA 9-1079, BIA 9-1100, BIA 9-1104 (each 3-3000 nmol/L) or BIA 9-1103 (10-3000 nmol/L) were added to the solution of S-COMT prepared from male rat liver, to which adrenaline (1000 μmol/L) was added 20 minutes later for 5-minute incubation at 37°C. The amount of metanephrine formed was determined by HPLC-ED. The half maximal inhibitory concentration (IC_{50}) of opicapone for S-COMT inhibition was 224 nmol/L, and that of metabolite BIA 9-1079 and BIA 9-1104 was 429 nmol/L and 128 nmol/L, respectively. Neither BIA 9-1103 nor BIA 9-1100 exhibited S-COMT inhibition.

3.1.2 *In vivo* studies

3.1.2.1 Inhibition of COMT in the peripheral and central nervous systems in normal animals (CTD 4.2.1.1-2, 3, and 6)

A single oral dose of opicapone (0.03-3 mg/kg), entacapone (0.3-30 mg/kg), or vehicle (0.05% carboxymethylcellulose [CMC]) was administered to male rats (n = 4-12/group). Adrenaline (1000 μmol/L) was added to liver homogenates isolated from rats 3 hours after administration. After incubation at 37°C for 5 minutes, the amount of metanephrine formed was determined by HPLC-ED. Opicapone and entacapone inhibited liver COMT activity in a dose-dependent manner, with a half maximal effective concentration (ED_{50}) of 0.9 and 7.5 mg/kg, respectively.

Oral doses of opicapone (3 mg/kg/day) or vehicle (0.5% CMC) were administered to male rats (n = 3-8/group) for 5 days. Adrenaline (1000 μmol/L) was added to homogenates of the livers, or supernatant of the hemolyzed erythrocytes isolated from rats at 3 hours, or 1, 2, 3, or 7 days after the last dose. After 5-minute incubation at 37°C, the amount of metanephrine formed was determined by HPLC-ED. The inhibition of COMT activity was 84% for the liver and 47% for erythrocytes 3 hours after the last dose of opicapone. One day after the last dose of opicapone, the inhibition of liver COMT activity was 61%, while 7 days later, liver COMT activity level was similar to that of the control. Erythrocyte COMT activity level 1 day after the last opicapone dose was similar to that of the control.

Oral doses of opicapone (3 or 30 mg/kg/day) or vehicle (0.5% CMC) were administered to male rats (n = 4/group) for 5 days. Livers were harvested 3 hours after the last dose, and the expression levels of messenger ribonucleic acid (mRNA) in liver COMT were measured by quantitative polymerase chain reaction (PCR). The amount of proteins in S-COMT and membrane-bound (MB) COMT was measured by Western blot. The expression levels of mRNA in COMT, and the amounts of S-COMT and MB-COMT proteins in the liver in the opicapone group were similar to those of the control group.

Oral doses of opicapone (1, 10, or 100 mg/kg/day) or vehicle (0.2% hydroxypropyl methylcellulose [HPMC]) were administered to female cynomolgus monkeys (n = 3/group) for 14 days. Venous blood was collected 1, 2, 4, and 24 hours after the first dose, and 24 hours after the last dose. Protocatechuic acid, a methyl accepting substrate (160 μmol/L), and S-(5'-adenosyl)-L-methionine (SAM) p-toluenesulfonate salt, a methyl donor substrate (192.81-194.18 μmol/L as a total concentration of ^{14}C-labeled and unlabeled) were added to the supernatant of hemolyzed erythrocytes. After 2-hour incubation at 37°C, the reaction product concentrations were measured by liquid scintillation counter. A 4-treatment, 4-period crossover design including the vehicle group was used. The maximum inhibition of erythrocyte COMT activity up to 24 hours post-first dose of opicapone was 13% at 1 mg/kg/day, 76% at 10 mg/kg/day, and 93% at 100 mg/kg/day. The area under the effect-time curve up to 24 hours post-dose ($AUEC_{0\text{-}24h}$) of erythrocyte COMT activity was significantly lower in the opicapone groups at ≥10 mg/kg/day than in the control group. The inhibition of erythrocyte COMT activity 24 hours post-last dose was significantly greater in the opicapone groups at ≥10 mg/kg/day than in the control group.

A single oral dose of opicapone (3 mg/kg), entacapone (3 mg/kg), or vehicle (0.5% CMC) was administered to male rats (n = 4-12/group). In the opicapone group, livers, kidneys, and erythrocytes were isolated 0.25 to 48 hours post-dose, and brains 0.5 to 9 hours post-dose. In the entacapone group, livers and brains were isolated 0.5 to 24 hours post-dose. To the homogenates of isolated livers, kidneys, and brains, and the supernatant of hemolyzed erythrocytes, adrenaline (1000 μmol/L [liver, kidney, and erythrocytes]; 100 μmol/L [brain]) was added. After incubation at 37°C for 5 minutes (liver, kidney), 15 minutes (brain), or 10 minutes (erythrocytes), the amount of metanephrine formed was determined by HPLC-ED. Up to 8 hours post-dose of opicapone, liver and kidney COMT activity was inhibited by ≥79% as compared with the control group. Liver COMT activity inhibition was 14% and kidney COMT activity inhibition was 30% 48 hours post-dose. The time course of

erythrocyte COMT activity was similar to that of liver and kidney COMT activities. Up to 1 hour post-dose of entacapone, liver COMT activity was inhibited by ≥68% as compared with the control group, and the inhibitory effect was no longer observed by 6 hours post-dose. Neither opicapone nor entacapone inhibited brain COMT activity.

3.1.2.2 Effects on rat plasma levodopa concentration (CTD 4.2.1.1-3)

Levodopa (12 mg/kg/day) and benserazide (3 mg/kg/day) were orally administered to male rats (n = 6-8/group) for 3 days. Two hours before levodopa/benserazide treatment, opicapone (3 mg/kg) was orally administered on Day 2, and vehicle (0.5% CMC) was orally administered on Days 1 and 3. On each day, dialysate samples were collected at 20-minute intervals from 40 minutes before the levodopa/benserazide dose to 380 minutes post-dose, and plasma concentrations of levodopa and 3-*O*-methyldopa (3-OMD) were determined by HPLC-ED. The AUC of plasma levodopa was 1.9-fold on Day 2 and 1.3-fold on Day 3 as compared to Day 1. In contrast, the plasma 3-OMD AUC was 17% on Day 2 and 63% on Day 3 as compared to Day 1. The C_{max} of plasma levodopa was 1.5-fold on Day 2 and 1.4-fold on Day 3 as compared to Day 1.

3.1.2.3 Effects on rat brain levodopa concentrations (CTD 4.2.1.1-3)

Opicapone (3 mg/kg) or vehicle (0.5% CMC) was orally administered to male rats (n = 4-11/group). The brain was isolated from each animal 1, 2, 7, 12, or 24 hours after the dose, and brain concentrations of levodopa, 3-OMD, 3,4-dihydroxyphenylacetic acid (DOPAC), dopamine, and homovanillic acid (HVA) were determined by HPLC-ED. One hour prior to brain isolation, levodopa (12 mg/kg/day) and benserazide (3 mg/kg/day) were orally administered to all animals. As compared with the control group, brain levodopa concentrations increased significantly in the opicapone group 7 hours post-dose onward, up to 3.1-fold by 12 hours post-dose. Brain 3-OMD concentrations were significantly lower in the opicapone group than in the control group 2 hours post-dose onward. As compared with the control group, brain DOPAC, dopamine, and HVA concentrations increased significantly in the opicapone group 7 hours post-dose onward, 12 hours post-dose onward, and between 7 to 12 hours respectively.

3.1.2.4 Effects on levodopa metabolism in monkeys (CTD 4.2.1.1-7)

Opicapone (100 mg/kg/day) or vehicle (0.2% HPMC) was orally administered to male and female cynomolgus monkeys (n = 3-4/group) for 14 days, and 23 hours after the last dose, levodopa (12 mg/kg/day) and benserazide (3 mg/kg/day) were orally administered. Venous blood samples and dialysate samples from the dorsal striatum, substantia nigra, and prefrontal cortex were collected over time from before the levodopa/benserazide dose to 360 minutes post-dose. The samples were analyzed for levodopa, 3-OMD, DOPAC, and HVA concentrations using HPLC-ED. The $AUC_{0\text{-}6h}$ of plasma levodopa concentrations was significantly higher in the opicapone group, 2.0 times that in the control group. The $AUC_{0\text{-}6h}$ of levodopa concentrations in striatum in the opicapone group was 1.7 times that in the control group, with no significant difference. The $AUC_{0\text{-}6h}$ of 3-OMD concentrations in plasma and the striatum was lower in the opicapone group as compared with that in the control group. The $AUC_{0\text{-}6h}$ of DOPAC and HVA concentrations in the striatum in the opicapone group was similar to that in the control group. In the substantia nigra and prefrontal cortex, the $AUC_{0\text{-}6h}$ of levodopa

concentrations was higher in the opicapone group than in the control group, while the $AUC_{0\text{-}6h}$ of 3-OMD concentrations was lower in the opicapone group than in the control group.

3.1.2.5 Effects on monkey models of PD (CTD 4.2.1.1-8)

To female cynomolgus monkeys (n = 25), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) 0.2 mg/kg/day was administered intravenously every day for a maximum of 14 days until the animals started exhibiting PD-like symptoms according to the Primate Parkinsonism Motor Rating Scale (PRMRS). To 10 of the animals showing symptoms persisting for ≥4 weeks from onset, opicapone (100 mg/kg/day) or vehicle (0.2% HPMC) was orally administered for 14 or 15 days; and for 5 days from Day 15 or 16, levodopa (6, 9, 12, 18, or 24 mg/kg/day) and benserazide (1.5, 2.25, 3, 4.5, or 6 mg/kg/day) were administered orally in a stepwise dose escalating manner in combination with opicapone (100 mg/kg/day) or vehicle (0.2% HPMC). The animals were evaluated for symptoms according to the PPMRS (once daily during the monotherapy; 1, 2, 3, 4, and 6 hours after each dose during the combination therapy) and for locomotor activity in the cage (once each in Days 1-3, Days 7-10, and Days 14-15 during the monotherapy; 1, 2, 3, 4, and 6 hours after each dose during the combination therapy). The study was performed in a 2-period crossover manner with the opicapone and control groups. The results in the monotherapy period indicated no significant differences in the PPMRS or locomotor activity between the opicapone and control groups. In the combination period, the PPMRS showed decreased severity in a manner depending on the dose of levodopa/benserazide both in the opicapone and control groups, with significantly low severity in the opicapone group as compared with the control group at levodopa 18 mg/kg/day and benserazide ≥4.5 mg/kg/day. In the combination period, locomotor activity increased in a manner depending on the dose of levodopa/benserazide both in the opicapone and control groups, and was significantly high in the opicapone group as compared with the control group at levodopa 18 mg/kg/day and benserazide ≥4.5 mg/kg/day.

3.2 Secondary pharmacodynamics

3.2.1 Inhibitory effect on binding to molecular targets (CTD 4.2.1.2-1 [reference data], 4.2.1.2-2 [reference data])

The binding affinity of opicapone (10 μmol/L) and BIA 9-1103 (10 μmol/L) for receptors, transporters, and enzymes (a total of 113 molecular targets) was analyzed. Enzymes that were inhibited by approximately ≥50% by opicapone or BIA 9-1103 as compared with baseline were evaluated for inhibitory activity at 0.03 to 100 μmol/L. Opicapone inhibited binding of PP2A and ZAP70 to the substrates by 77% and 49%, respectively, and ligand binding to translocator protein (TSPO) by 82%. The IC_{50} of opicapone for the enzyme activity was 45 μmol/L for PP2A and 17 μmol/L for ZAP70. On the other hand, BIA 9-1103 inhibited the binding of phosphodiesterase (PDE) 5A1 to the substrate by 55%, and ligand binding to TSPO by 88%. The IC_{50} of BIA 9-1103 for the enzyme activity of PDE5A1 was 63 μmol/L. No other receptors, transporters, or enzymes were inhibited by ≥50% by opicapone (10 μmol/L) or BIA 9-1103 (10 μmol/L).

3.3 Safety pharmacology

Table 4 shows the results of safety pharmacology studies.

Table 4. Summary of data from safety pharmacology studies

Organ system	Test system	Test parameter/method	Dose	Route of administration	Findings	CTD
Central nervous system	Wistar rats (4 males, 1 group)	Irwin test	Single dose of 0, 30, 300, or 1000 mg/kg	Oral	30 mg/kg Excitation ≥300 mg/kg Sedation, head seizure, bowel movement, diarrhea 1000 mg/kg pupillary dilation, nasal bleeding, decreased respiration	4.2.1.3-1
Cardiovascular system	hERG transfected HEK293 cells (3 specimens each/dose level)	hERG current	0, 3, 10, 30,or 100 μmol/L	*In vitro*	Inhibited hERG current by 12.7% at 30 μmol/L and by 25.9% at 100 μmol/L IC_{50} = 388.9 μmol/L	4.2.1.3-2
			BIA 9-1103 0, 1, 3, 10, or 30 μg/mL	*In vitro*	No effects	4.2.1.3-9
	Cardiac muscle cells from beagle dogs (6 specimens each/dose level)	Amplitude of action potential, resting membrane potential, maximum depolarization rate, APD 30, APD 60, APD 90, APT (APD 90−APD 60), reverse frequency dependence	0, 0.1, 1, or 10 μg/mL	*In vitro*	10 μg/mL Prolonged APD 90 and prolonged APT	4.2.1.3-3
			0, 1, 3, or 10 μg/mL	*In vitro*	1 μg/mL Decreased resting membrane potential 10 μg/mL Shortened APD 60 and APD 90	4.2.1.3-4
	Cardiac muscle cells from beagle dogs (6 specimens each/dose level)	Amplitude of action potential, resting membrane potential, maximum depolarization rate, APD 30, APD 60, APD 90, APT (APD 90−APD 60), reverse frequency dependence	BIA 9-1103 0, 1, 3, or 10 μg/mL	*In vitro*	10 μg/mL Prolonged APD 60 and APD 90	4.2.1.3-10
	Beagle dogs (4 males, 1 group)	Blood pressure, heart rate, electrocardiography (telemetry)	Single dose of 0, 60, 200, or 600 mg/kg	Oral	No effects	4.2.1.3-5
Respiratory system	Wistar rats (8 males, 1 group)	Plethysmography	Single dose of 0, 30, 300, or 1000 mg/kg	Oral	≥300 mg/kg Decreased respiration, prolonged inspiration time, prolonged exhalation time, prolonged relaxation time	4.2.1.3-6
Renal/urinary system	Wistar rats (12 males, 1 group)	Urine volume, urinary pH, urinary creatinine, urinary sodium, urinary potassium	Single dose of 0, 30, 300, or 1000 mg/kg	Oral	No effects	4.2.1.3-7
Gastrointestinal system	Wistar rats (8 males, 1 group)	Intestinal transport	Single dose of 0, 30, 300, and 1000 mg/kg	Oral	No effects	4.2.1.3-8

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamics

The applicant’s explanation about the primary pharmacodynamic action of opicapone:

In *in vitro* studies, opicapone inhibited human and rat COMT with a K_i of 0.02 and 0.2 nmol/L, respectively. In *in vivo* studies, while opicapone did not inhibit brain COMT, it inhibited liver, kidney, and erythrocyte COMT in rats and erythrocyte COMT in monkeys. Opicapone administered in combination with levodopa/benserazide increased levodopa concentrations in plasma and brain in normal animals, and improved PD-like symptoms and locomotor activity in monkey models of PD. The doses which were demonstrated to be effective in rats (3 mg/kg) and monkeys (100 mg/kg) inhibited erythrocyte COMT activity by 88% in rats and 93% in monkeys, with opicapone C_{max} of 0.427 μg/mL in rats and 1.08 to 1.21 μg/mL in monkeys that were close to the inhibition of erythrocyte COMT activity (88%) and C_{max} of opicapone (0.97 μg/mL) following a single oral dose of 25 mg, the recommended clinical dose in humans. The plasma concentration of BIA 9-1079, a metabolite in monkeys, is approximately 70% (C_{max}) of unchanged opicapone, and the IC_{50} values of BIA 9-1079 for rat COMT activity inhibition is 429 nmol/L, which is approximately twice that of opicapone, 224 nmol/L. These indicate not only opicapone but also BIA 9-1079 contributes to COMT inhibition in monkeys. However, based on the levels of contribution to COMT inhibition by opicapone and BIA 9-1079, the efficacy of opicapone in humans may be extrapolated from the relationship between the plasma opicapone concentrations and COMT inhibition in monkeys described above.

Based on the above, it is considered that opicapone inhibits peripheral COMT, increases levodopa levels in the brain, and helps improve the wearing-off phenomenon associated with levodopa therapy.

PMDA's view:
As observed in the *in vitro* and *in vivo* studies, opicapone inhibits COMT activity, increases plasma and brain levodopa concentrations in its combination use with levodopa/benserazide, and improves PD-like symptoms and locomotor activity in animal models of PD. The findings indicate that opicapone inhibits peripheral COMT and increases levodopa concentrations in the brain, and consequently helps alleviate the wearing-off phenomenon.

3.R.2 Duration of COMT inhibitory effect by opicapone

PMDA asked the applicant to explain the mechanism of the duration of the peripheral COMT inhibitory effect by opicapone from pharmacokinetic (PK) and pharmacological viewpoints.

The applicant's explanation:
In the pharmacokinetic point of view, the plasma elimination half-life after the last dose was 1.67 hours following oral daily dose of opicapone 25 mg administered to humans for 10 days, which was comparable to 1.73 hours following oral dose of entacapone 200 mg administered 3 times daily for 1 day. In the pharmacological view, following a single oral dose of opicapone 3 mg/kg or entacapone 3 mg/kg to rats,[2)] liver

[2)] The C_{max} following a single oral dose of opicapone 3 mg/kg in rats was estimated to be 0.44 times that following a single oral dose of the recommended clinical dose of opicapone 25 mg in humans. The C_{max} following a single oral dose of entacapone 3 mg/kg in rats was estimated to be 1.91 times that following a single oral dose of the recommended clinical dose of entacapone100 mg in humans.

COMT activity was inhibited by ≥79% up to 8 hours post-dose in the opicapone group as compared with the control group, whereas the entacapone group showed liver COMT activity recovering to the level equivalent to that in the control group by 6 hours post-dose. Based on the results of Study BIA-91067-124, a foreign phase I study which evaluated the duration of the erythrocyte COMT inhibitory effect, whether the differences in duration observed in the non-clinical studies would also be observed in humans was investigated. The 10-day multiple doses of oral opicapone 25, 50, or 75 mg QD revealed a ≥64% COMT activity inhibition from baseline by 24 hours post-last dose at all dose levels. In contrast, following oral doses of entacapone 200 mg TID for 1 day, COMT activity recovered to baseline levels by 7 hours post-last dose. These findings suggest that opicapone's COMT inhibitory effect lasted even after its elimination from blood while erythrocyte COMT activity recovers in response to the elimination of entacapone from blood.

Opicapone bound to form a complex with COMT is thought to dissociate from COMT after COMT methylates hydroxyl group in the catechol structure. The small dissociation constant (0.19 pmol/L) of the COMT-opicapone complex suggests that, due to its slow methylation product formation rate or dissociation rate after forming of the complex, opicapone can occupy the active center of the enzyme for longer time, and this mechanism may be contributory to long lasting COMT inhibitory effect of opicapone.

PMDA's view:
The submitted study results do not clearly explain a mechanism causing difference in duration of COMT inhibitory effect of these agents. However, the results from non-clinical and clinical studies indicate that opicapone has COMT inhibitory effect that is expected to last longer than that of entacapone. Yet, whether the once daily regimen of opicapone is appropriate in its clinical use should be assessed based on the clinical data [see Section "7.R.6 Dosage and administration"].

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The plasma concentrations of opicapone and its metabolite BIA 9-1079 (reduced *N*-oxide of opicapone) were measured by liquid chromatography with tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation for plasma concentrations of opicapone and BIA 9-1079 was 20 ng/mL for rats and monkeys. Radioactivity levels following the administration of ^{14}C-labeled opicapone were measured by liquid scintillation counter or quantitative whole-body autoradiography.

Unless otherwise specified, PK parameters are expressed as mean or mean ± standard deviation.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1, 2)

A single oral dose of ^{14}C-labeled opicapone 10 mg/kg was administered to male rats and male monkeys. Plasma radioactivity levels peaked 4 hours post-dose in rats (1561 ± 277 ng eq/g) and 0.25 hours post-dose in monkeys (1596 ± 620 ng eq/g). In both rats and monkeys, plasma radioactivity levels decreased over time and declined more gradually at 24 hours post-dose onward.

4.1.2 Repeated-dose studies

Table 5 shows PK parameters of opicapone and BIA 9-1079 following the oral administration of opicapone to male and female rats once daily for 26 weeks.

Table 5. PK parameters in rats following repeated oral doses of opicapone for 26 weeks

Dose (mg/kg)	Time point	Opicapone				BIA 9-1079			
		C_{max} (μg/mL)		$AUC_{0\text{-last}}$ (μg·h/mL)		C_{max} (μg/mL)		$AUC_{0\text{-last}}$ (μg·h/mL)	
		Male	Female	Male	Female	Male	Female	Male	Female
100	Day 1	4.14	4.29	17.47	14.02	1.86	1.45	19.73	11.95
	Week 13	8.82	10.80	15.01	12.41	1.20	1.05	16.35	7.53
	Week 26	7.19	7.66	14.95	11.27	1.14	0.97	15.12	7.58
500	Day 1	8.28	10.50	33.63	31.45	2.12	2.30	25.58	19.80
	Week 13	16.73	26.83	38.60	53.42	3.05	3.12	28.62	28.20
	Week 26	19.47	27.13	59.18	41.61	2.64	2.45	34.11	19.98
1000	Day 1	16.47	23.37	50.62	49.31	3.07	2.54	40.08	31.93
	Week 13	18.80	31.40	54.04	62.54	4.47	4.15	47.52	37.86
	Week 26	19.73	23.33	67.94	65.22	4.05	3.66	46.50	35.03

n = 3/time point

Table 6 shows PK parameters of opicapone and BIA 9-1079 following the oral administration of opicapone to male and female monkeys once daily for 52 weeks.

Table 6. PK parameters in monkeys following repeated oral doses of opicapone for 52 weeks

Dose (mg/kg)	Time point	Opicapone				BIA 9-1079			
		C_{max} (μg/mL)		$AUC_{0\text{-last}}$ (μg·h/mL)		C_{max} (μg/mL)		$AUC_{0\text{-last}}$ (μg·h/mL)	
		Male	Female	Male	Female	Male	Female	Male	Female
100	Day 1	1.08	1.21	1.39	1.33	0.85	0.72	4.04	3.32
	Week 13	0.50	0.75	0.65	0.83	0.91	0.77	4.17	2.84
	Week 52	1.04	1.26	1.65	2.27	1.36	1.21	6.42	6.47
300	Day 1	2.26	1.61	2.97	3.62	0.87	1.14	5.79	9.31
	Week 13	1.46	1.07	2.45	1.89	1.18	1.32	8.42	10.60
	Week 52	1.21	1.11	2.62	3.40	1.44	1.42	11.40	13.90
1000	Day 1	9.42	8.80	32.10	34.40	2.22	2.57	27.10	30.00
	Week 13	6.99	5.22	30.00	15.30	2.39	2.86	35.70	36.40
	Week 52	4.44	2.92	20.90	16.20	2.31	2.42	36.80	36.10

n = 4 to 6/time point

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3-1)

A single oral dose of ^{14}C-labeled opicapone 10 mg/kg was administered to male white rats to evaluate tissue distribution of radioactivity at 1, 4, 12, and 48 hours post-dose (n = 3/time point). Tissue radioactivity levels peaked 4 hours post-dose in the majority of tissues evaluated. Other than the gastrointestinal tract, the maximum radioactivity levels were higher in the following tissues as compared with those in blood: liver (12.3-fold the blood radioactivity level), renal cortex (7.27-fold), and renal medulla (6.49-fold). At the final evaluation time point of 48 hours post-dose, the radioactivity levels fell below the lower limit of quantitation

in many tissues; however, the radioactivity levels in the liver, renal cortex, renal medulla, and blood were approximately 50% of highest concentrations. Radioactivity levels in the brain remained below the lower limit of quantitation at all time points. The applicant explained that no tissue distribution studies were conducted in pigmented rats for following reasons: opicapone is an acidic compound, not a basic compound which generally has high affinity for melanin (e.g., *Drug Metab Rev.* 1984;15(5-6):1183-212, *Pharm Res.* 1990;7(9):935-41); and 4- to 52-week repeated dose toxicity studies in monkeys did not indicate toxicities caused by the administration of opicapone in the eye or skin, both of which are melanin-containing tissues.

4.2.2 Protein binding (CTD 4.2.2.3-2, 3)

To rat or monkey plasma, ^{14}C-labeled opicapone 0.3 to 30 μg/mL was added. Plasma protein binding was 99.5% to 99.8% in rats and 99.4% to 99.6% in monkeys.

To rat, dog, or monkey plasma, BIA 9-1103 (3-*O*-sulfate conjugate) 4 to 40 ng/mL was added. Plasma protein binding was 99.62% to 99.67% in rats, 99.52% to 99.63% in dogs, and 99.59% to 99.64% in monkeys.

4.2.3 Distribution in blood cells (CTD 4.2.2.3-2)

To blood from rats and monkeys, ^{14}C-labeled opicapone 0.3 to 30 μg/mL was added. Binding to blood cells was 0.0% to 2.4% in rats and 3.8% to 18.6% in monkeys.

4.2.4 Placental transfer (CTD 4.2.2.3-4)

A single oral dose of ^{14}C-labeled opicapone 10 mg/kg was administered to female rats on gestation day 17, and tissue radioactivity levels at 1, 4, 12, and 48 hours post-dose were evaluated. Radioactivity was distributed to fetuses, and fetal radioactivity levels were 0.02 to 0.86 times the maternal plasma radioactivity levels.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 4.2.2.4-1-3)

Opicapone 20 μmol/L, uridine 5'-diphosphoglucuronic acid (UDPGA), nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and 3'-phosphoadenosine-5'-phosphosulfate (PAPS) were added to mouse and rat liver S9 fractions for 1-hour incubation at 37°C. In both animal species, the metabolites of opicapone detected were BIA 9-1079, BIA 9-1103, BIA 9-1105 (3-*O*-sulfate conjugate of BIA 9-1079), BIA 9-1106 (3-*O*-glucuronide of opicapone), and BIA 9-1107 (3-*O*-glucuronide of BIA 9-1079).

Opicapone 10 μmol/L and PAPS were added to rat, dog, and monkey liver S9 fractions for 1-hour incubation at 37°C. The metabolic activity of opicapone for BIA 9-1103 was 86.2 fmol/mg/min in rats, 91.8 fmol/mg/min in dogs, and 74.5 fmol/mg/min for monkeys.

Opicapone 10 μmol/L or BIA 9-1079 10 μmol/L was added to rat liver homogenates, mouse and rat S-COMT, and mouse and rat liver S9 fractions for incubation in the presence of *S*-adenosyl methionine at 37°C for 30 to 120 minutes (with rat liver homogenates), 60 to 120 minutes (with S-COMT), or 60 minutes (with S9) to

investigate the metabolism of opicapone and BIA 9-1079 to methylated products. In rat liver homogenates, methylated opicapone and BIA 9-1079 were detected. In mouse and rat S-COMT, and mouse and rat liver S9 fractions, opicapone was primarily metabolized to BIA 9-1100 (3-*O*-methyl opicapone), while BIA 9-1079 was primarily metabolized to BIA 9-1101 (3-*O*-methyl BIA 9-1079).

4.3.2 *In vivo* metabolism (CTD 4.2.2.4-4, 5)

Following a single oral dose of opicapone 10 mg/kg to male rats, main metabolites detected in plasma were BIA 9-1100, BIA 9-1106, and BIA 9-1103.

Following repeated oral doses of opicapone 1000 mg/kg once daily to male and female monkeys, main metabolites detected in plasma were BIA 9-1106, BIA 9-1079, and BIA 9-1103.

4.4 Excretion

4.4.1 Excretion in urine, feces, and expired air (CTD 4.2.2.2-1, 2)

A single oral dose of ^{14}C-labeled opicapone 10 mg/kg or a single intravenous dose of ^{14}C-labeled opicapone 1 mg/kg was administered to male rats (n = 4/group). Cumulative excretion of radioactivity (percentage of the administered radioactivity) up to 120 hours post-dose was 4.0% in urine, 92.3% in feces, and 1.5% in expired air in the oral dose group and 5.7% in urine, 72.8% in feces, and 2.2% in expired air in the intravenous dose group.

A single oral dose of ^{14}C-labeled opicapone 10 mg/kg or a single intravenous dose of ^{14}C-labeled opicapone 1 mg/kg was administered to male rats (n = 4/group). Cumulative excretion of radioactivity (percentage of the administered radioactivity) up to 168 hours post-dose was 5.1% in urine and 76.0% in feces in the oral dose group and 6.2% in urine and 55.6% in feces in the intravenous dose group.

4.4.2 Excretion in milk (CTD 4.2.2.5-1)

A single oral dose of ^{14}C-labeled opicapone was administered to female rats (n = 3) at 11 days postpartum to evaluate radioactivity levels in breast milk and plasma at 1, 4, 12, and 48 hours post-dose. The radioactivity level in milk peaked at 12 hours post-dose. Radioactivity levels in breast milk were 0.509- to 1.08-times that in plasma, and decreased over time as the plasma radioactivity decreased.

4.5 Pharmacokinetic interactions (CTD 5.3.3.4-18)

Opicapone (100 μg/mL) was added to iron solutions (0.1-10 mmol/L) for 60-minute incubation at 37°C. Insoluble precipitates formed in the iron solutions, and the solubility of opicapone decreased in an iron concentration-dependent manner.

4.R Outline of the review conducted by PMDA

4.R.1 Tissue distribution

The tissue distribution study in rats revealed high radioactivity levels in the liver and kidney. PMDA asked the applicant to explain potential safety problems posed to humans.

The applicant's explanation:

In repeated-dose toxicity studies in rats and monkeys, no serious toxicity findings were noted in the liver, and no toxicity findings were noted in the kidneys [see Section "5.2 Repeated-dose toxicity"]. Therefore, it is considered that the accumulation of opicapone or its metabolites in the liver and kidneys is unlikely to pose safety problems to humans.

PMDA concluded that the applicant's point about the unlikeliness of safety problems to humans posed by the accumulation of opicapone or its metabolites in the liver and kidneys is reasonable based on the submitted data from non-clinical toxicity studies.

5. Toxicity and Outline of the Review Conducted by PMDA

The results of the following toxicity studies of opicapone were submitted: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other studies (toxicity studies in combination with levodopa/carbidopa, photosafety, metabolite toxicity, and impurity toxicity studies).

5.1 Single-dose toxicity

Single dose toxicity studies in mice, rats, dogs, miniature pigs, and monkeys were conducted (Table 7).

Table 7. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male and female mice (CD-1)	Oral	250, 1000, 2000	2000; hunchback position, piloerection	>2000	4.2.3.1-1
Male and female rats (SD)	Oral	250, 1000, 2000	No findings	>2000	4.2.3.1-2
Male and female rats (SD)	IV	1, 5, 10	Death at 10 (female, 1 of 1 animal); collapse, labored ventilation, seizure ≥1; decrease in locomotor activity, hunchback position, reddish urine, soiled perineal region 5; ataxic gait, labored ventilation, tachypnea	10	Reference 4.2.3.1-3
Male and female dogs (beagle)	Oral	**Single ascending dose study** 100→200→400→600→800→1000 **7-day repeated-dose study** 1000	No findings	>1000	Reference 4.2.3.1-4
Male and female miniature pigs (Gottingen)	Oral	**Single, 3-day ascending dose study** 100→200→400→800→1000 **14-day repeated-dose study** 1000	No findings	>1000	Reference 4.2.3.1-5
Male and female cynomolgus monkeys	Oral	**Single, 3-day ascending dose study** 100→200→400→600→1000 **7-day repeated-dose study** 1000	No findings	>1000	Reference 4.2.3.1-6

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in rats (4, 13, and 26 weeks), dogs (4 weeks), and monkeys (4, 13, and 52 weeks) (Table 8). According to the applicant, observed opicapone-associated changes in the digestive organs and liver were not considered to cause clinical problems because the changes in the digestive organs were not accompanied by clinical symptoms, and those in the liver did not cause histopathological changes in the liver. In repeated oral-dose toxicity studies, exposures ($AUC_{0\text{-}24h}$) at no-observed adverse effect levels (NOAELs) in rats for 26 weeks and monkeys for 52 weeks (500 mg/kg/day for rats; 1000 mg/kg/day for monkeys) were 59.2 μg·h/mL and 20.9 μg·h/mL, respectively, which are 23.9-fold and 8.4-fold, respectively, as compared with the exposures ($AUC_{0\text{-}24h}$, 2.48 μg·h/mL) at the maximum clinical dose (25 mg/day).

Table 8. Repeated-dose toxicity studies

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	CTD
Male/female rats (Wistar)	Oral	4 weeks (once daily)	0,[a] 100, 500, 1000	No findings	1000	4.2.3.2-2
Male/female rats (Wistar)	Oral	13 weeks (once daily)	0,[a] 100, 500, 1000	No findings	1000	4.2.3.2-3
Male/female rats (Wistar)	Oral	26 weeks (once daily)	0,[a] 100, 500, 1000	1000; prothrombin time (PT) prolongation, high total bilirubin, high lactate dehydrogenase (LDH), acanthosis in the stomach, parakeratosis, erosion in the fore-stomach	500	4.2.3.2-5
Male/female dogs (beagle)	Oral	4 weeks (once daily)	0,[b] 60, 200, 600	No findings	600	Reference 4.2.3.2-6
Male/female cynomolgus monkeys	Oral	4 weeks (once daily)	0,[a] 100, 300, 1000	No findings	1000	4.2.3.2-7
Male/female cynomolgus monkeys	Oral	13 weeks (once daily)	0,[a] 100, 300, 1000	No findings	1000	4.2.3.2-8
Male/female cynomolgus monkeys	Oral	52 weeks (once daily)	0,[a] 100, 300, 1000	No findings	1000	4.2.3.2-9

a, HPMC solution
b, empty gelatin capsules

5.3 Genotoxicity

Genotoxicity studies consisted of an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosomal aberration study in human peripheral blood lymphocytes, and an *in vivo* micronucleus assay using mice. While the findings from the *in vitro* chromosomal aberration study were suggestive of potential induction of numerical aberration opicapone, the *in vivo* micronucleus assay returned a negative result. Therefore, the applicant concluded that opicapone is unlikely to be genotoxic in clinical use (Table 9).

Table 9. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Test result	CTD
In vitro	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 17, 50, 167, 500, 1667, 5000	Negative	4.2.3.3.1-1
	Chromosomal aberration study in human peripheral blood lymphocytes	Human lymphocytes	S9 −/+ (−, 5 and 25 hours; +, 5 hours)	−S9, 0,[a] 78-313 +S9, 0,[a] 78-313	Positive	4.2.3.3.1-2
In vivo	Micronucleus assay in mice	Mice (CD-1)		Male, 0,[b] 450, 900, 1800 Female, 0,[b] 1800	Negative	4.2.3.3.2-1

a, DMSO
b, HPMC solution

5.4 Carcinogenicity

Long-term carcinogenicity studies were conducted in mice and rats, and the results did not indicate that opicapone is carcinogenic (Table 10).

Table 10. Carcinogenicity studies

Test system	Route of administration	Treatment period	Major lesions	Dose	(mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	CTD
					0[a]	0[a]	100	500/375	1000/750		
				N	M/F 56[b]	M/F 50	M/F 65[b]	M/F 65[b]	M/F 65[b]		
Male and female mice (CD-1)	Oral	2 years	Neoplastic lesions							1000/750	4.2.3.4.1-3
			Oligodendro-glioma in the brain	M	0	0	0	1	0		
				F	0	0	0	0	0		
			Luteoma	M	—	—	—	—	—		
				F	0	0	0	2	0		
			Hibernoma in the adrenal gland	M	1	0	0	1	0		
				F	0	0	0	1	1		
			Non-neoplastic lesions[c]		High eosinophil percentage, high hemoglobin concentration distribution width, high reticulocyte count, high glucose level, high potassium level						
Male and female rats (Wistar)	Oral	2 years	Major lesions	Dose	(mg/kg/day)					1000	4.2.3.4.1-4
					0[a]	0[a]	100	500	1000		
				N	M/F 51	M/F 51	M/F 51	M/F 51	M/F 51		
			Neoplastic lesions		None						
			Non-neoplastic lesions		PT prolongation, high AST/LDH/phosphorus/albumin levels, low liver and spleen weights						

a, HPMC solution
b, Due to increased deaths, satellite animals (6 in the control group and 15 in the opicapone group) were added to the evaluation group.
c, The fatal cases were often attributable to treatment errors, and the applicant inferred that these changes had caused the deaths.

5.5 Reproductive and developmental toxicity

A study on fertility and early embryonic development to implantation in male and female rats, embryo-fetal development studies in rats and rabbits, and a study for effects on pre-and post-natal development, including maternal function, in rats were conducted (Table 11). In the rat study on pre-and post-natal development and maternal function, some pups in the post-weaning stage were sacrificed moribund and necropsied due to deteriorated condition.

Table 11. Reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	CTD
Fertility and early embryonic development to implantation	Male and female rats (Wistar)	Oral	(Males) 28 days before mating until 1 day before necropsy (once daily) (Females) 14 days before mating until gestation day 6 (once daily)	0,[a] 150, 375, 1000	Parent animals: none Fertility, early embryonic development: none	Parent animals (general toxicity), 1000 (fertility and early embryonic development), 1000	4.2.3.5.1-2
Embryo-fetal development	Female rats (Wistar)	Oral	Gestation days 6-17 (once daily)	0,[a] 150, 375, 1000	Dams: none Fetuses: ≥375; hyper-ossification in phalanges[b] 1000; persistent left umbilical artery,[c] increased heterogeneous ossification in the frontal bone[b]	Dams, 1000 Embryo and fetuses, 1000	4.2.3.5.2-2
	Female rabbits (NZW)	Oral	Gestation days 6-18 (once daily)	0,[a] 100, 175, 225	Dams: Death[d] at 175 (1 of 20 animals), at 225 (2 of 20 animals), pleural effusion/ascites retention ≥175; decreased body weight, decreased food consumption Fetuses: ≥100; dwarf fetuses,[b] skeletal anomalies[b]	Dams, 100 Embryo and fetuses, 225	4.2.3.5.2-5
Effects on pre- and postnatal development, including maternal function	Female rats (Wistar)	Oral	Dams: Gestation days 6 to lactation day 20 (once daily)	0,[a] 150, 375, 1000	Dams: none Live F1 offspring: Death[e] at 1000 (2 of 20 animals)	Dams, 1000 Live F1 offspring (development), 375 (function), 1000	4.2.3.5.3-1

a, HPMC solution
b, The applicant concluded that the values are within the historical range and are toxicologically insignificant.
c, The applicant viewed it as a mutational change rather than teratogenic and is toxicologically insignificant.
d, The animals were sacrificed moribund and necropsied before completing the study because of continuous cessation of food intake.
e, The animals were sacrificed moribund and necropsied before completing the study because of deteriorated condition.

5.6 Other studies

5.6.1 Toxicity studies in combination with levodopa/carbidopa

A repeated-dose toxicity study of opicapone in combination with levodopa/carbidopa was conducted in rats. The combination of opicapone with levodopa/carbidopa did not intensify the toxicity of opicapone (Table 12).

Table 12. Toxicity studies in combination with levodopa/carbidopa

Test system	Route of administration	Treatment period	Dose[a] (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	CTD
Male and female rats (Wistar)	Oral	13 weeks (once daily)	0/0/0[b] Opicapone group: 1000/0/0 Levodopa/carbidopa group: 0/20/5 Combination group: 1000/20/5, 1000/50/12.5, 1000/120/30	≥1000/20/5; hypertrophy of acinar cell of the parotid gland,[c] hyperplasia of brown adipose tissue in the exorbital lacrimal gland[c] ≥1000/50/12.5; collapse,[c] unkempt fur,[c] salivation,[c] hypertrophy of acinar cell of submandibular gland/exorbital lacrimal gland[c] 1000/120/30; decreased body weight gain (male), abnormal hematological test,[d] low thymus weight (male),[d] high ovary weight (female),[d] mammary gland hyperplasia (male), vacuolation of acinar cell in the pancreas (female)	1000/50/12.5	4.2.3.7.7-5

a, The dose is shown in the order of opicapone/levodopa/carbidopa.
b, HPMC solution
c, The applicant concluded that the change is attributable to the pharmacological action of levodopa/carbidopa and is toxicologically insignificant.
d, The applicant concluded that, due to no histopathological changes, the finding is toxicologically insignificant.

5.6.2 Photosafety

An *in vitro* phototoxicity study and a skin photosensitization study in guinea pigs were conducted. The applicant concluded that opicapone is not phototoxic, skin photosensitizing, skin sensitizing, skin photo-irritating, or skin irritating (Table 13).

Table 13. Photosafety studies

Type of study	Test system	Testing method	Major findings	CTD
Phototoxicity	Mouse fibroblast cells Balb/c 3T3	Cells were exposed to opicapone 3.91-500 μg/mL with or without ultraviolet (UV)-A irradiation, and the percentage of cell survival was calculated.	Not phototoxic	4.2.3.7.7-1
Skin photosensitization	Female guinea pigs (Hartley)	According to the adjuvant-strip method, animals were administered with complete Freund's adjuvant, transdermal of opicapone 50%, and underwent photosensitization to UV-A (approximately 10 J/cm^2) and UV-B (approximately 1.8 J/cm^2) irradiations, followed by transdermal administration of opicapone 10%, 15%, 25%, or 50% and UV-A (approximately 10 J/cm^2) irradiation for photoinduction.	No findings	4.2.3.7.7-2

5.6.3 Toxicity studies of metabolites

Single dose toxicity studies and genotoxicity studies of BIA 9-1079 and BIA 9-1103, metabolites of opicapone, were conducted (Tables 14 and 15).

Table 14. Single dose toxicity studies of metabolites

Analyte	Test system	Route of administration	Dose (mg/kg/day)	Major findings	Approximate lethal dose (mg/kg/day)	CTD
BIA 9-1079	Male and female mice (CD-1)	Oral	300, 1000, 2000	2000; increased respiration rate, hunchback position, piloerection	>2000	Reference 4.2.3.7.5-1
BIA 9-1079	Male and female rats (SD)	Oral	300, 1000, 2000	2000; decreased locomotor activity, increased respiration rate	>2000	Reference 4.2.3.7.5-2
BIA 9-1079	Male and female rats (SD)	Intravenous	2, 8	Death at 8 (female, 1 of 3 animals) 2; reddish urine 8; decreased locomotor activity, labored ventilation, reddish nasal discharge	8	Reference 4.2.3.7.5-3

Table 15. Genotoxicity studies of metabolites

Analyte	Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) dose (mg/kg/day)	Test result	CTD
BIA 9-1079	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 1.7-500	Negative	4.2.3.7.5-5
	In vitro	Chromosomal aberration study in human peripheral blood lymphocytes	Human lymphocytes	S9 −/+ (−, 5 and 25 hours; +, 5 hours)	−S9, 0,[a] 31-250 and 8-31 + S9, 0,[a] 31-250	Negative	4.2.3.7.5-7
	In vivo	Micronucleus assay in mice	Mice (CD-1)		0,[b] 500, 1000, 2000	Negative	4.2.3.7.5-8
BIA 9-1103	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0, 17-5000	Negative	4.2.3.7.5-4
	In vitro	Chromosomal aberration study in human peripheral blood lymphocytes	Human lymphocytes	S9 −/+ (−, 5 and 25 hours; +, 5 hours)	−S9, 0,[a] 78-625 and 625-3000 +S9, 0,[a] 625-3000	Negative	4.2.3.7.5-6

a, DMSO
b, Methylcellulose (MC) solution

5.6.4 Toxicity studies on impurities

None of the impurities were detected in an amount exceeding the specified threshold for safety verification according to the “Guidelines on Impurities in New Drug Substances” (PMSB/ELD Notification No. 1216001, dated December 16, 2002) and “Guidelines on Impurities in New Drug Products” (PMSB/ELD Notification No. 0624001, dated June 24, 2003).

To evaluate the genotoxicity of impurities derived from the manufacturing process of drug substance and degradation products contained in the drug product, *in silico* analyses using toxicology programs such as Derek Nexus and Leadscope or genotoxicity studies were performed by referencing the ICH M7 Guidelines (Table 16). Based on the analyses, 7 kinds of impurities were classified as Class 2 impurities. However, the applicant

concluded that the clinical use of opicapone would not lead to the consumption of these impurities exceeding the daily limits specified in the ICH M7 Guidelines.

Table 16. Genotoxicity studies of impurities

Analyte	Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate)	Test result	CTD
Impurity A	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 31.25-1000	Negative	4.2.3.7.6-3
Impurity B	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 12.5-400	Positive	4.2.3.7.6-4
Impurity C	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 17-5000	Negative	4.2.3.7.6-5
Impurity D	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 3.3-3333.3	Positive	4.2.3.7.6-6
Impurity E	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Positive	4.2.3.7.6-7
Impurity F	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Negative	4.2.3.7.6-8
Impurity G	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Negative	4.2.3.7.6-9
Impurity H	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Positive	4.2.3.7.6-10
Impurity I	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Positive	4.2.3.7.6-11
Impurity J	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Negative	4.2.3.7.6-12
Impurity K	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Negative	4.2.3.7.6-13
Impurity L	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Positive	4.2.3.7.6-14
	In vitro	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[b] 5-5000	Negative	4.2.3.7.6-15
Impurity M	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Positive	4.2.3.7.6-16
Impurity N	*In vitro*	Bacterial reverse mutation assay (Ames test)	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E. coli*: WP2*uvr*A	S9 −/+	0,[a] 5-5000	Positive	4.2.3.7.6-17

a, DMSO
b, acetone

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the non-clinical toxicity studies identified no findings with potential concerns in clinical use.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Unless otherwise specified, PK parameters are expressed as mean or mean ± standard deviation.

6.1 Summary of biopharmaceutic studies and associated analytical methods

In foreign phase III studies, i.e., Studies BIA-91067-301 (Foreign Study 301) and BIA-91067-302 (Foreign Study 302), capsule formulations (5, 25, and 50 mg) were used, and in a Japanese phase II study, i.e., Study ONO-2370-02 (Japanese Study 02), tablet formulations (TAB-A; 25 and 50 mg) were used. Subsequently, newly formulated tablets (TAB-B; 25 and 50 mg) were manufactured with differently formulated [redacted] from TAB-A, and TAB-B 50 mg tablets were used in the food effect study (Study ONO-2370-03). While TAB-B 25 mg tablets were scored, unscored tablets were to-be-marketed.

Bioequivalence between TAB-A 25 mg and TAB-B 25 mg tablets and that between TAB-A 50 mg and TAB-B 50 mg tablets were demonstrated by dissolution studies in accordance with the Guideline for Bioequivalence Studies for Formulation Changes. Bioequivalence among the to-be-marketed formulation, TAB-A 25 mg tablets, and TAB-B 25 mg tablets were also demonstrated by dissolution studies in accordance with the Guideline for Bioequivalence Studies for Formulation Changes.

Plasma opicapone concentrations were determined by LC-MS/MS, and the lower limit of quantitation was 10 ng/mL.

6.1.1 Food effect study (Study ONO-2370-03, CTD 5.3.1.1-1)

A 2-treatment, 2-period crossover study was conducted in 12 Japanese healthy adults to investigate the food effect on the PK of opicapone following a single oral dose of opicapone 50 mg under fasted or fed conditions (washout period, 7 days).

The geometric mean ratios [90% confidence interval (CI)] of C_{max} and $AUC_{0-\infty}$ of opicapone administered under fed conditions relative to these administered under fasted conditions were 0.53 [0.45, 0.62] and 0.57 [0.51, 0.64], respectively. The t_{max} of opicapone did not differ between the fed dose and the fasted dose.

6.1.2 Bioequivalence study (Part I of Study ONO-2370-01, dose proportionality study, CTD 5.3.1.2-1, 5.3.3.1-5 [reference data])

A 2-treatment, 2-period crossover study was conducted in 48 Japanese healthy adults to evaluate bioequivalence of TAB-A and the capsule formulation following a single oral dose of opicapone 25 or 50 mg in either dosage form (washout period, ≥28 days).

The geometric mean ratios [90% CI] of C_{max} and AUC_{0-last} of opicapone in TAB-A relative to that in capsules were 1.24 [1.12, 1.37] and 1.18 [1.10, 1.27], respectively, in the opicapone 25 mg cohort and 1.42 [1.25, 1.62]

and 1.28 [1.15, 1.43], respectively, in the opicapone 50 mg cohort. The geometric mean ratios [90% CI] of dose-adjusted C_{max} and $AUC_{0\text{-last}}$ of opicapone in TAB-A 25 mg to those in TAB-A 50 mg were 0.95 [0.84, 1.08] and 0.97 [0.84, 1.11], respectively.

Pharmacodynamic parameters on S-COMT activity, namely, maximum S-COMT inhibition (E_{max}) and AUEC from time zero to the last quantifiable concentration ($AUEC_{last}$) following the administration of TAB-A did not differ significantly from those following the administration of the capsule formulation.

6.2 Clinical pharmacology

6.2.1 *In vitro* studies using human biological samples

6.2.1.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-2, 4.2.2.3-3, 5.3.2.1-1)

When ^{14}C-labeled opicapone (0.3-30 μg/mL), BIA 9-1103 (4-40 ng/mL), or BIA 9-1079 (4-40 ng/mL) was added to human plasma, the protein binding was 99.9% for opicapone, 99.51% to 99.68% for BIA 9-1103, and 99.92% to 99.97% for BIA 9-1079.

When ^{14}C-labeled opicapone (0.3-30 μg/mL) was added to human blood, no distribution of opicapone was observed in blood cells.

6.2.1.2 Drug interactions mediated by plasma protein binding (CTD 4.2.2.3-2, 5.3.2.1-2)

Opicapone (0.3-30 μg/mL) was added to human plasma in the presence of warfarin (5 μg/mL), diazepam (5 μg/mL), digoxin (5 μg/mL), tolbutamide (20 μg/mL), or BIA 9-1103 (0.3-30 μg/mL). The plasma protein binding of opicapone was not affected by these agents, and opicapone did not affect the plasma protein binding of these agents.

BIA 9-1103 (0.3-30 μg/mL) was added to human plasma in the presence of warfarin (5 μg/mL), diazepam (5 μg/mL), digoxin (5 μg/mL), or tolbutamide (20 μg/mL). The plasma protein binding of these agents was not affected by BIA 9-1103.

6.2.1.3 *In vitro*

6.2.1.3.1 Identification of SULT isoforms involved in opicapone metabolism (CTD 5.3.2.2-1)

Opicapone 10 μmol/L was added to the human sulfotransferase (SULT) isoform (SULT1A1*1, SULT1A1*2, SULT1A2, SULT1A3, SULT1B1, SULT1E1, and SULT2A1) expression systems for 60-minute incubation at 37°C. Sulfate conjugation of opicapone (formation of BIA 9-1103) was detected primarily in SULT1A1*1 and SULT1A1*2 expression systems.

6.2.1.3.2 Identification of UGT isoforms involved in opicapone metabolism (CTD 5.3.2.2-3)

Opicapone 1 to 250 μmol/L was added to human UDP-glucuronosyltransferase (UGT) isoform (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, and UGT2B17) expression systems for 0 to 60-minute incubation at 37°C. UGT-mediated metabolism of

opicapone was observed in UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10, and UGT2B7 expression systems. Opicapone had high affinity for UGT1A7, UGT1A9, UGT1A1, and UGT2B7 with a K_m of 1.658, 13.7, 18.0, and 20.6 μmol/L, respectively.

6.2.1.3.3 Identification of CYP isoforms involved in opicapone metabolism (CTD 5.3.2.2-4)

Opicapone 5 μmol/L was added to human cytochrome P450 (CYP) isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) expression systems for 60-minute incubation at 37°C. The metabolism of opicapone was primarily observed in the CYP3A4 expression system.

6.2.1.3.4 Catechol-*O*-methylation (CTD 4.2.2.4-3)

Opicapone 10 μmol/L or BIA 9-1079 10 μmol/L was added to human liver S9 fractions for 60-minute incubation at 37°C in the presence of SAM. No methylation of opicapone or BIA 9-1079 was detected.

6.2.1.4 Enzyme inhibition (CTD 5.3.2.2-5 to 7)

Using human liver microsomes and the substrates for CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4), the inhibitory effects of opicapone (0.03-10 μg/mL), BIA 9-1103 (0.1-30 μg/mL), and BIA 9-1079 (0.03-10 μg/mL) on the metabolism of the substrates of CYP isoforms were evaluated. Opicapone, BIA 9-1103, and BIA 9-1079 showed inhibitory effects on CYP2C8 and CYP2C9. K_i of opicapone on CYP2C8 and CYP2C9 was 0.9 and 18 μg/mL, respectively; IC_{50} of BIA 9-1103 6.70 and 20.7 μg/mL, respectively; and K_i of BIA 9-1079 0.19 and 1.47 μg/mL, respectively. Opicapone, BIA 9-1103, and BIA 9-1079 did not show time-dependent inhibitory effects on any CYP isoform.

6.2.1.5 Enzyme induction (CTD 5.3.2.2-9 to 12)

Opicapone (1-10 μg/mL), BIA 9-1079 (1-10 μg/mL), or BIA 9-1103 (3-30 μg/mL) was added to human hepatocytes for 72-hour incubation at 37°C to evaluate the induction of CYP1A2, CYP2C9, and CYP3A4 by opicapone or BIA 9-1079 and induction of CYP1A2, CYP2B6, and CYP3A4 by BIA 9-1103. Opicapone, BIA 9-1079, or BIA 9-1103 did not induce any CYP isoforms studied.

Opicapone, BIA 9-1103, or BIA 9-1079 (each 10 μmol/L) was added to HepaRG cells for 72-hour incubation at 37°C. Opicapone, BIA 9-1079, or BIA 9-1103 did not induce any CYP isoforms studied (CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4).

6.2.1.6 Transporters (CTD 5.3.2.3-1 to 6, 5.3.2.3-8, 9)

Opicapone (50 μmol/L) or BIA 9-1103 (50 μmol/L) was added to Madin-Darby canine kidney (MDCK) cells for 30-minute incubation at 37°C. The apparent permeability coefficient was 1.0×10^{-5} cm/s for opicapone and 4.4×10^{7} cm/s for BIA 9-1103.

Opicapone (10 μmol/L) was added to Caco-2 cells for 60- and 120- minute incubation at 37°C. The efflux ratio of opicapone ($P_{app\ B \rightarrow A}/P_{app\ A \rightarrow B}$) was 4.3 (60 minutes) and 2.4 (120 minutes). In the presence of DNP (agent for

uncoupling of oxidative phosphorylation in mitochondria), the $P_{app\ A\rightarrow B}$ of opicapone increased as compared with that in the absence of DNP. In addition, Ko 143 (breast cancer resistance protein [BCRP] inhibitor) or MK571 (multidrug resistance-associated protein [MRP] 2 inhibitor) increased the $P_{app\ A\rightarrow B}$ of opicapone and reduced the $P_{app\ B\rightarrow A}$ of opicapone. No effect of verapamil (P-glycoprotein [P-gp] inhibitor) on membrane permeability of opicapone was observed.

Opicapone (10 μmol/L) was added to Caco-2 cells for 30-minute incubation at 37°C. Opicapone uptake into cells was greater at pH 6.5 than at pH 7.4. Opicapone uptake into cells was inhibited by estrone-3-sulfate, pravastatin, diclofenac, valproic acid, and quercetin, all of which are organic anion transporting polypeptide (OATP) 2B1 substrates.

Opicapone (1-100 μmol/L) was added to CHO cells expressing human OATP1B1. Opicapone uptake into OATP1B1-expressing cells was equivalent to that of the control cells.

Opicapone (1 μg/mL) was added to HEK293 cells expressing human OATP1B3. Opicapone uptake into OATP1B3-expressing cells was 4.4-fold that into the control cells, and the intracellular uptake was inhibited by rifampicin (OATP1B3 inhibitor).

Opicapone (5 μmol/L) was added to MDCK II cells expressing human P-gp for 60 minute-incubation in the presence or absence of elacridar (P-gp inhibitor) at 37°C. The efflux ratio was 0.78 and 3.5, respectively.

Opicapone (1-10 μg/mL) was added to MDCK II cells expressing human BCRP for 120 minute-incubation at 37°C. The efflux ratio of opicapone was 6.6 to 11.1.

BIA 9-1103 (10 μg/mL) was added to human OATP1B1-expressing HEK293 cells, and BIA 9-1103 (1 μg/mL) was added to human OATP1B3-expressing HEK293 cells. BIA 9-1103 uptake into cells was 78.4- and 42.6-fold that into the control cells, and the intracellular uptake was inhibited by rifampicin (OATP1B1 and OATP1B3 inhibitor) in either HEK293 cells.

BIA 9-1103 (1-10 μg/mL) was added to MDCK II cells expressing human P-gp or BCRP. The efflux ratio of BIA 9-1103 was 0.5 to 0.8 (P-gp) and 1.6 to 3.9 (BCRP).

Using MDCK II cells expressing human P-gp, BCRP, multidrug and toxin extrusion (MATE) 1, MATE2-K, or organic cation transporter (OCT) 2, CHO cells expressing organic anion transporter (OAT) 1 or OCT1, HEK293 cells expressing OATP1B1, OATP1B3, or OAT3, or membrane vesicles prepared from bile salt export pump (BSEP)-expressing cells, the inhibitory effects of opicapone (0.04-30 μg/mL; except for P-gp, 100 μmol/L and BCRP, 30 μg/mL) on the transport of the substrates for each transporter were evaluated. Opicapone inhibited OAT1 (IC_{50} = 9.18 μg/mL), OAT3 (IC_{50} = 4.36 μg/mL), OATP1B1 (IC_{50} = 0.45 μg/mL), OATP1B3 (IC_{50} = 1.40 μg/mL), MATE2-K ($IC_{50} \approx$ 30 μg/mL), and BSEP (IC_{50} = 12.28 μg/mL). The inhibitory

effects of BIA 9-1103 (0.04-30 μg/mL; except for P-gp and BCRP, 30 μg/mL) on the transport of the substrate for each transporter were evaluated in a similar manner. BIA 9-1103 inhibited OAT1 (IC_{50} = 13.20 μg/mL), OAT3 (IC_{50} = 2.55 μg/mL), OATP1B1 (IC_{50} = 2.80 μg/mL), and OATP1B3 (IC_{50} = 7.51 μg/mL).

6.2.2 Studies in healthy adults

6.2.2.1 Multiple-dose study in Japanese and non-Japanese healthy adults (Study BIA-91067-126, CTD 5.3.3.3-4)

Opicapone 5, 25, or 50 mg was administered orally once daily to healthy adults (40 Japanese and 36 non-Japanese) under fasted conditions. Table 17 shows the PK parameters of opicapone.

Table 17. PK parameters following multiple-dose administration of opicapone

Dose (mg)	Subject	N	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-t} (ng·h/mL)
Day 1					
5	Japanese	14	176 ± 93.6	2.0	319 ± 154
	Non-Japanese	13	182 ± 64.5	2.0	267 ± 113
25	Japanese	14	797 ± 323	2.0	1886 ± 692
	Non-Japanese	11	794 ± 392	2.0	2013 ± 800
50	Japanese	12	1736 ± 381	2.0	4438 ± 1151
	Non-Japanese	11	1540 ± 493	3.0	3727 ± 1726
Day 10					
5	Japanese	14	276 ± 130	2.0	441 ± 139
	Non-Japanese	13	226 ± 110	1.0	349 ± 169
25	Japanese	13	959 ± 273	2.0	2222 ± 407
	Non-Japanese	12	774 ± 361	2.0	2024 ± 820
50	Japanese	12	1785 ± 431	2.0	4464 ± 932
	Non-Japanese	11	1550 ± 655	1.5	3999 ± 1770

a, median

6.2.2.2 Multiple-dose study in non-Japanese healthy adults (Study BIA-91067-128, CTD 5.3.1.1-3)

Opicapone 50 mg (1 50 mg-capsule) was administered orally once daily for 12 days to non-Japanese healthy adults (n = 28) under fasted or fed conditions, and food effect on the PK and pharmacodynamics of opicapone was evaluated. Opicapone was administered after a meal only on Day 10 and under fasted conditions on the rest of the days.

The geometric mean ratios of C_{max} and AUC_{0-last} of the fed opicapone dose (Day 10) relative to a fasted dose (Day 9) and the 90% CI were 0.3821 [0.3262, 0.4476] and 0.6870 [0.5876, 0.8007], respectively. The t_{max} (median) of opicapone was delayed under fed conditions (6 hours) as compared with that under fasted conditions (2 hours).

Pharmacodynamic parameters on S-COMT activity, namely, E_{max}%, $AUEC_{0-24h}$, and minimum S-COMT inhibition (E_{min}%), under fasted conditions did not differ greatly from those under fed conditions.

6.2.2.3 Mass balance study (Study BIA-91067-130, CTD 5.3.3.1-4 [reference data])

Following a single oral dose of ^{14}C-labeled opicapone 100 mg to 7 non-Japanese healthy adults under fasted conditions, 5.3% of the administered dose was recovered in urine, 70.4% in feces, and 20.5% in expired air up to 504 hours post-dose. The main metabolite found in plasma was BIA 9-1103, with the AUC equivalent to 58.6% of the radioactivity in plasma.

6.2.3 A study in patients (Study BIA-91067-201, CTD 5.3.4.2-1 [reference data])

A 4-treatment, 4-period crossover study was conducted in non-Japanese patients (n = 10) with PD. A single oral dose of opicapone 25, 50, or 100 mg, or placebo was administered under fasted conditions in combination with the preparation (QD) of levodopa/carbidopa (100/25 mg) or levodopa/benserazide (100/25 mg) (washout period, ≥10 days).

Table 18 shows the PK parameters of opicapone following a single oral dose of opicapone under fasted conditions in combination with levodopa/carbidopa or levodopa/benserazide preparation.

Table 18. PK parameters of opicapone following single oral dose of opicapone

Dose (mg)	N	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
25	10	320 ± 183	2.0	979 ± 432[b]	1.06 ± 0.444[b]
50	10	590 ± 245	2.0	1835 ± 780 [c]	0.950 ± 0.335[c]
100	10	816 ± 289	2.0	2919 ± 1242	1.34 ± 0.601

a, median; b, n = 7; c, n = 9

The effects of opicapone on the PK parameters of levodopa and 3-OMD in plasma when administered in combination with levodopa/carbidopa or levodopa/benserazide preparation were investigated (Table 19).

Table 19. The effects of opicapone on PK parameters of levodopa and 3-OMD in plasma

	C_{max}	AUC_{0-6h}
Effects on levodopa PK parameters (compared to concomitant placebo)		
Opicapone 25 mg	0.91 [0.75, 1.12]	1.04 [0.83, 1.29]
Opicapone 50 mg	1.08 [0.88, 1.33]	1.16 [0.93, 1.45]
Opicapone 100 mg	1.29 [1.06, 1.58]	1.35 [1.08, 1.68]
Effects on 3-OMD PK parameters (compared to concomitant placebo)		
Opicapone 25 mg	0.89 [0.74, 1.07]	0.86 [0.72, 1.03]
Opicapone 50 mg	0.84 [0.70, 1.01]	0.84 [0.70, 1.01]
Opicapone 100 mg	0.71 [0.59, 0.85]	0.71 [0.59, 0.85]

Geometric mean ratio [90% CI]

6.2.4 Population pharmacokinetic analyses and population pharmacokinetic/pharmacodynamic analyses (CTD 5.3.3.5-1)

Population pharmacokinetic (PPK) analyses were performed using plasma opicapone concentration data (n = 304, 3752 time points) obtained from studies in healthy adults: foreign phase I studies (Studies BIA-91067-119, BIA-91067-120, BIA-91067-125, BIA-91067-126, and BIA-91067-128) and Japanese phase I studies (Studies ONO-2370-01 and ONO-2370-03).

The PK of opicapone was described by a 1-compartment model with first-order absorption and lag time. Potential covariates that may affect the PK of opicapone were meal conditions (fasted or fed), dosage form (capsules or tablets), administration time (morning or evening), study region (Japan, Hawaii, or France), race (Japanese or non-Japanese), sex, and body weight. After examination, food conditions and dosage form were chosen as covariates for absorption rate constant (KA) of opicapone, food conditions, study region, and dosage form for relative bioavailability (F1), and body weight for oral clearance (CL/F).

Using the final PPK model developed, the C_{max}, AUC_{0-24h}, and C_{24h} of opicapone at steady state were estimated for oral multiple doses of opicapone administered under fasted conditions to Japanese subjects (tablets) and non-Japanese subjects (capsules) once daily. (Table 20).

Table 20. Estimated PK parameters of opicapone at steady state[a]

Dose (mg)	Subjects	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	C_{24h} (ng/mL)
12.5	Japanese	528 ± 234	1230 ± 430	24.3 ± 21.5
	Non-Japanese	247 ± 105	700 ± 243	21.1 ± 14.0
25	Japanese	1060 ± 471	2390 ± 825	25.3 ± 23.5
	Non-Japanese	495 ± 219	1270 ± 446	23.7 ± 21.5
50	Japanese	2150 ± 933	4710 ± 1680	29.8 ± 36.6
	Non-Japanese	967 ± 402	2390 ± 804	26.7 ± 27.0

a, estimated values obtained by simulation with PPK parameters in the final PPK model

Based on plasma levodopa AUC_{0-24h} data before and after the administration of opicapone (n = 142, 220 time points) obtained from studies in healthy adults, the foreign phase I study (Study BIA-91067-124) and Japanese phase I study (Study ONO-2370-01), PPK/pharmacodynamic analyses were performed to investigate the relationship between the $AUC_{0-\infty}$ of opicapone and AUC_{0-24h} of plasma levodopa. The opicapone PK/pharmacodynamic model was described by an E_{max} model, with model parameters of E_0 (plasma levodopa AUC_{0-24h} at baseline), E_{max} (maximum response to levodopa), AUC_{50} (opicapone $AUC_{0-\infty}$ which produces 50% of E_{max} response), and Hill coefficient.

Covariates that may significantly affect pharmacodynamic parameters (E_0 and E_{max}) related to plasma levodopa AUC_{0-24h} were analyzed, and inter-study difference was identified as a significant covariate for E_0. Based on the levodopa AUC_{0-24h} estimated using the final PPK/pharmacodynamic model, the ratio of levodopa AUC_{0-24h} pre- to post-opicapone dose (AUCR) was calculated, and the relationship between opicapone $AUC_{0-\infty}$ and AUCR was evaluated by study. Although inter-study difference was a specified covariate potentially significantly influential to E_0, the extent of increase in levodopa AUCR associated with increase in opicapone $AUC_{0-\infty}$ was similar between Study BIA-91067-128 and Study ONO-2370-01.

6.2.5 Studies on intrinsic factors

6.2.5.1 Effect of age (Study BIA-91067-105, CTD 5.3.3.3-2 [reference data])

Oral opicapone 30 mg was administered to 12 non-Japanese healthy elderly subjects (mean ± standard deviation age of 69.5 ± 4.3 years) and 12 non-Japanese healthy younger subjects (31.7 ± 5.9 years) under fasted

conditions once daily for 7 days. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}24h}$ of opicapone in elderly to those in younger subjects were 1.09 [0.88, 1.34] and 1.12 [0.88, 1.42], respectively on Day 1, and 1.19 [0.92, 1.55] and 1.28 [0.99, 1.64], respectively on Day 7.

6.2.5.2 Effect of hepatic impairment (Study BIA-91067-106, CTD 5.3.3.3-3 [reference data])

A single oral dose of opicapone 50 mg was administered to 8 non-Japanese subjects with moderate hepatic impairment (Child-Pugh B) and 8 non-Japanese subjects with normal hepatic function under fasted conditions. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}\infty}$ of opicapone in subjects with moderate impairment to those with normal hepatic function were 1.89 [1.44, 2.49] and 1.84 [1.35, 2.50], respectively. The plasma protein binding of opicapone did not differ between subjects with hepatic impairment and those with normal hepatic function.

6.2.6 Drug interactions

6.2.6.1 Pharmacokinetic drug interactions

6.2.6.1.1 Levodopa/DCI preparations (Studies BIA-91067-117, BIA-91067-118, Part II of ONO-2370-01, CTD 5.3.1.2-1, 5.3.3.4-10 [reference data], 11 [reference data])

The effects of opicapone on the PK of levodopa, 3-OMD, and carbidopa in plasma were studied in 18 non-Japanese healthy adults. Subjects received a single oral dose of levodopa/carbidopa 100/25 mg preparation under fasted conditions either alone, 1 hour after the dose of opicapone 50 mg (1 hour staggered dosing), or simultaneously with opicapone 50 mg (simultaneous dosing), and the results are presented in Table 21.

Table 21. Effects of opicapone on plasma PK parameters of levodopa, 3-OMD, and carbidopa

	C_{max}	$AUC_{0\text{-}\infty}$
Effects on levodopa PK parameters		
1-hour staggered dosing/monotherapy	1.03 [0.89, 1.19]	1.10 [1.00, 1.20]
Simultaneous dosing/monotherapy	1.12 [0.97, 1.30]	1.03 [0.94, 1.13]
1-hour staggered dosing/simultaneous dosing	0.92 [0.80, 1.06]	1.09 [1.01, 1.16]
Effects on 3-OMD PK parameters		
1-hour staggered dosing/monotherapy	0.69 [0.66, 0.72]	0.68 [0.64, 0.73]
Simultaneous dosing/monotherapy	0.80 [0.76, 0.84]	0.78 [0.73, 0.84]
1-hour staggered dosing/simultaneous dosing	0.86 [0.82, 0.90]	0.87 [0.81, 0.95]
Effects on carbidopa PK parameters		
1-hour staggered dosing/monotherapy	1.05 [0.89, 1.25]	1.05 [0.93, 1.20]
Simultaneous dosing/monotherapy	1.06 [0.89, 1.26]	1.09 [0.96, 1.25]
1-hour staggered dosing/simultaneous dosing	1.00 [0.84, 1.18]	0.97 [0.85, 1.10]

Geometric mean ratio [90% CI]

The effects of opicapone on the PK of levodopa, 3-OMD, and carbidopa in plasma were studied in 49 non-Japanese healthy adults. Subjects received oral placebo or opicapone 5, 15, or 30 mg under fasted conditions once daily for 28 days. On Day 21, 1 hour after the dose of opicapone or placebo, a single oral dose of levodopa/carbidopa 100/25 mg preparation was administered under fasted conditions. On Day 28, 1 hour after the dose of opicapone or placebo, a single oral dose of levodopa/benserazide 100/25 mg preparation was administered under fasted conditions. Tables 22 and 23 show the results.

Table 22. Effects of opicapone on plasma PK parameters of levodopa and 3-OMD following the dose of levodopa/carbidopa preparation

	C_{max}	$AUC_{0-\infty}$[a]
Effects on levodopa PK parameters (compared with concomitant placebo		
Opicapone 5 mg	1.23 [0.98, 1.55]	1.77 [1.41, 2.22]
Opicapone 15 mg	1.15 [0.92, 1.45]	1.62 [1.29, 2.03]
Opicapone 30 mg	0.96 [0.76, 1.21]	1.50 [1.20, 1.88]
Effects on 3-OMD PK parameters (compared with concomitant placebo)		
Opicapone 5 mg	0.67 [0.51, 0.88]	0.67 [0.49, 0.90]
Opicapone 15 mg	0.34 [0.26, 0.45]	0.34 [0.25, 0.45]
Opicapone 30 mg	0.24 [0.18, 0.32]	0.20 [0.15, 0.27]

Geometric mean ratio [90% CI]
a, AUC_{0-last} for 3-OMD

Table 23. Effects of opicapone on plasma PK parameters of levodopa and 3-OMD following the dose of levodopa/benserazide preparation

	C_{max}	$AUC_{0-\infty}$[a]
Effects on levodopa PK parameters (compared with concomitant placebo)		
Opicapone 5 mg	1.25 [0.90, 1.73]	1.67 [1.36, 2.06]
Opicapone 15 mg	0.97 [0.70, 1.34]	1.42 [1.15, 1.75]
Opicapone 30 mg	1.09 [0.79, 1.51]	1.72 [1.40, 2.12]
Effects on 3-OMD PK parameters (compared with concomitant placebo)		
Opicapone 5 mg	0.54 [0.41, 0.71]	0.56 [0.43, 0.74]
Opicapone 15 mg	0.28 [0.21, 0.37]	0.28 [0.21, 0.37]
Opicapone 30 mg	0.23 [0.18, 0.31]	0.23 [0.17, 0.30]

Geometric mean ratio [90% CI]
a, AUC_{0-last} for 3-OMD

Opicapone 5, 10, 25, or 50 mg was administered to 80 Japanese healthy adults under fasted conditions orally once daily at bedtime for 11 days. Oral levodopa/carbidopa 100/10 mg preparation were administered under fasted conditions 3 times daily on the day before the first dose and on the following day of the last dose of opicapone Table 24 shows the effects of opicapone on plasma PK of levodopa, 3-OMD, and carbidopa.

Table 24. Effects of opicapone on plasma PK parameters of levodopa, 3-OMD, and carbidopa

	C_{max} (1st dose)	C_{max} (2nd dose)	C_{max} (3rd dose)	AUC_{0-24h}
Effects on levodopa PK parameters (compared with before dosing opicapone)				
Opicapone 5 mg	0.85 [0.73, 1.00]	1.43 [1.17, 1.75]	1.10 [0.97, 1.26]	1.16 [1.10, 1.21]
Opicapone 10 mg	1.06 [0.87, 1.28]	1.56 [1.35, 1.82]	1.24 [1.10, 1.40]	1.26 [1.23, 1.30]
Opicapone 25 mg	1.12 [1.00, 1.26]	1.15 [0.98, 1.36]	1.15 [1.00, 1.32]	1.51 [1.44, 1.57]
Opicapone 50 mg	1.01 [0.86, 1.19]	1.40 [1.16, 1.68]	1.21 [1.03, 1.42]	1.60 [1.54, 1.66]
Effects on 3-OMD PK parameters (compared with before dosing opicapone)				
Opicapone 5 mg	0.49 [0.45, 0.53]	0.52 [0.49, 0.56]	0.54 [0.51, 0.56]	0.54 [0.51, 0.57]
Opicapone 10 mg	0.37 [0.34, 0.40]	0.40 [0.37, 0.43]	0.41 [0.38, 0.44]	0.41 [0.38, 0.44]
Opicapone 25 mg	0.21 [0.17, 0.26]	0.20 [0.19, 0.22]	0.22 [0.21, 0.24]	0.21 [0.19, 0.22]
Opicapone 50 mg	—	0.16 [0.15, 0.17]	0.17 [0.16, 0.18]	0.15 [0.14, 0.17]
Effects on carbidopa PK parameters (compared with before dosing opicapone)				
Opicapone 5 mg	1.22 [1.05, 1.42]	1.48 [1.39, 1.58]	1.12 [1.04, 1.21]	1.28 [1.21, 1.35]
Opicapone 10 mg	1.30 [1.16, 1.46]	1.45 [1.32, 1.60]	0.96 [0.89, 1.04]	1.23 [1.15, 1.32]
Opicapone 25 mg	1.53 [1.32, 1.78]	1.17 [1.03, 1.33]	0.88 [0.81, 0.97]	1.20 [1.11, 1.29]
Opicapone 50 mg	1.50 [1.28, 1.76]	1.51 [1.38, 1.66]	0.90 [0.81, 1.00]	1.34 [1.22, 1.47]

Geometric mean ratio [90% CI]

6.2.6.1.2 Repaglinide (Study BIA-91067-115, CTD 5.3.3.4-8 [reference data])

A total of 27 non-Japanese healthy adults received a single oral dose of repaglinide 0.5 mg under fasted conditions or 1.25 hours after a single oral dose of opicapone 25 mg under fasted conditions. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of repaglinide coadministered with opicapone to repaglinide alone were 1.31 [1.14, 1.51] and 1.09 [1.02, 1.17], respectively.

6.2.6.1.3 Warfarin (Study BIA-91067-127, CTD 5.3.3.4-15 [reference data])

A total of 20 non-Japanese healthy adults received a single oral dose of warfarin 25 mg under fasted conditions alone or with opicapone 50 mg under fasted conditions following 7-days opicapone treatment (the loading dose of oral opicapone 475 mg once daily for 2 days followed by oral opicapone 50 mg once daily for 5 days). The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of *S*-warfarin coadministered with opicapone to warfarin alone were 1.005 [0.843, 1.199] and 0.883 [0.800, 0.974], respectively, while those of *R*-warfarin were 0.978 [0.823, 1.163] and 0.872 [0.787, 0.967], respectively.

The geometric mean ratios [90% CI] of maximum international normalised ratio (INR_{max}) and AUC for international normalised ratio (prothrombin time) up to 144 hours post-dose ($INRAUC_{144h}$) of warfarin coadministered with opicapone to warfarin alone were 0.919 [0.877, 0.963] and 0.921 [0.882, 0.962], respectively.

6.2.6.1.4 Acetaminophen (Study BIA-91067-125, CTD 5.3.3.4-14 [reference data])

A total of 28 non-Japanese healthy adults received a single oral dose of opicapone 50 mg under fasted conditions alone or 1.5 hours after the third dose of acetaminophen 1 g (3 doses of acetaminophen were administered 6 hours apart). The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of opicapone coadministered with acetaminophen to opicapone alone were 1.13 [1.01, 1.25] and 1.15 [1.08, 1.23],

respectively. The geometric mean ratios of C_{max} and $AUC_{0-\infty}$ of BIA 9-1103 following the opicapone coadministered with acetaminophen to those following opicapone alone were 0.88 [0.82, 0.94] and 0.89 [0.83, 0.95], respectively; and those of BIA 9-1106 were 1.68 [1.53, 1.83] and 1.83 [1.59, 2.11], respectively.

The geometric mean ratios [90% CI] of E_{max} and $AUEC_{0-24h}$ of S-COMT activity following the opicapone coadministered with acetaminophen to those following opicapone alone were 1.03 [1.00, 1.05] and 0.95 [0.92, 0.98], respectively.

6.2.6.1.5 Rasagiline (Studies BIA-91067-112 and BIA-91067-113, CTD 5.3.3.4-5 [reference data], 6 [reference data])

A total of 24 non-Japanese healthy adults received a single oral dose of rasagiline 1 mg under fasted conditions alone, 1 hour after the administration of a single oral dose of opicapone 50 mg under fasted conditions, or coadministered with opicapone 50 mg simultaneously under fasted conditions. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of rasagiline coadministered with opicapone (1 hour after opicapone) to rasagiline alone were 1.00 [0.86, 1.16] and 1.02 [0.96, 1.09], respectively, while those of rasagiline coadministered simultaneously with opicapone to rasagiline alone were 1.01 [0.87, 1.17] and 1.02 [0.96, 1.09], respectively.

A total of 25 non-Japanese healthy adults received a single oral dose of opicapone 50 mg under fasted conditions alone, a single oral dose of opicapone 50 mg 1 hour before a single oral dose of rasagiline 1 mg under fasted conditions, or a single oral dose of opicapone 50 mg coadministered simultaneously with rasagiline 1 mg under fasted conditions. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of opicapone coadministered with rasagiline (1 hour before rasagiline) to opicapone alone were 1.12 [0.98, 1.27] and 1.07 [0.94, 1.23], respectively, while those of opicapone coadministered simultaneously with rasagiline to opicapone alone were 1.00 [0.88, 1.14] and 1.05 [0.91, 1.20], respectively.

6.2.7 QT/QTc evaluation (Study BIA-91067-111, CTD 5.3.4.1-1 [reference data])

The effects on QT interval following the administration of a single oral dose of opicapone 50 or 800 mg, placebo, or moxifloxacin 400 mg under fasted conditions were investigated in 64 non-Japanese healthy adults.

Following the administration of a single oral dose of opicapone 50 or 800 mg under fasted conditions, C_{max} was 496.8 ± 227.0 ng/mL (50 mg) and 3854.8 ± 1671.7 ng/mL (800 mg), respectively, $AUC_{0-\infty}$ was 1417 ± 608 ng·h/mL (50 mg) and 11823 ± 6117 ng·h/mL (800 mg), respectively, and t_{max} (median) was 2 hours (50 mg) and 1.5 hours (800 mg), respectively.

The changes from baseline in individually corrected QT interval (QTcI) following opicapone 50 or 800 mg were analyzed. The upper limits of the 95% CI for the difference between opicapone and placebo in QTcI (ΔΔQTcI) were below 10 milliseconds at all time points. The lower limits of the 95% CI for ΔΔQTcI following

the administration of moxifloxacin were higher than 5 milliseconds at 1 to 4 hours post-dose, around the approximate t_{max}.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK of opicapone between Japanese and non-Japanese populations

The applicant's explanation about the differences in the PK of opicapone between Japanese and non-Japanese populations:

The PK parameters of opicapone in Japanese subjects were similar to those in Caucasian subjects following the administration of oral opicapone 25 or 50 mg in the foreign phase I study conducted in Hawaii targeting Japanese and Caucasian healthy adults (Study BIA-91067-126) (Table 17). In contrast, in clinical studies conducted in France (Studies BIA-91067-119, BIA-91067-120, and BIA-91067-125) enrolling non-Japanese (primarily Caucasian) healthy adults and using a formulation identical to that in Study BIA-91067-126, the C_{max} and $AUC_{0\text{-last}}$ of opicapone following a single oral dose of opicapone 25 or 50 mg tended to be lower than those in Caucasian healthy adults in Study BIA-91067-126, suggesting regional differences in opicapone exposure (Table 25). Opicapone was shown to form an insoluble chelate with iron in the *in vitro* study [see Section "4.5 Pharmacokinetic interactions"] and the amounts of metal ions contained in food and drinking water may vary regionally. Given these, the regional difference in opicapone exposure may be attributable to different opicapone absorption due to different environmental factors including dietary habit.

Table 25. PK parameters of opicapone following a single oral dose of opicapone

Study	Study region	Dose (mg)	N	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng·h/mL)
BIA-91067-126	Hawaii	25	11[a]	794 ± 392	2013 ± 800
BIA-91067-119	France		27[a]	450 ± 156	1207 ± 414
BIA-91067-126	Hawaii	50	11[a]	1540 ± 493	3727 ± 1726
BIA-91067-119	France		28[b]	808 ± 302	2242 ± 1032
BIA-91067-120			28[a]	771 ± 184	2401 ± 778
BIA-91067-125			28[c]	895 ± 376	2416 ± 884

a, all subjects are Caucasian; b, 27 Caucasian, 1 mixed race;
c, 27 Caucasian, 1 American Indian or Alaska native

Study 302 was the foreign clinical study planned to be used for bridging in the development of opicapone in Japan. Because Study 302 was not conducted in Hawaii, differences in the PK of opicapone following a single oral dose of opicapone 25 or 50 mg between Japanese and non-Japanese populations were investigated (Table 26) using data from the following studies: clinical studies (Studies BIA-91067-119, BIA-91067-120, and BIA-91067-125), which were conducted in France in non-Japanese (mainly Caucasian) healthy adults using the capsule formulation used in Study 302; and clinical studies (BIA-91067-126 and ONO-2370-01), which were conducted in Hawaii or Japan in Japanese healthy adults using the capsule formulation used in Study 302 or TAB-A, the tablet formulation used in Japanese Study 02, the Japanese bridging study. The results showed that C_{max} and $AUC_{0\text{-last}}$ tended to be higher in Japanese subjects than in Caucasian subjects regardless of the formulation used, and the opicapone exposure in Japanese subjects following the TAB-A dose were approximately 2-fold that in Caucasian subjects following the capsule dose. In addition, PPK analyses based on Japanese and foreign clinical study also suggested that the level of multiple oral doses of TAB-A

administered to Japanese subjects would be approximately half the multiple oral doses of capsules administered to Caucasian subjects to attain an equivalent exposure (Table 20).

Based on the above, if an equal dose of opicapone is administered to Caucasian subjects and Japanese subjects under equivalent conditions to Study 302 used for bridging, and Japanese Study 02, the bridging study, opicapone exposure in Japanese will be approximately 2-fold that in Caucasians.

Table 26. PK parameters of opicapone following single oral dose of opicapone

Formulation	Dose (mg)	Subject	N	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng·h/mL)
TAB-A	25	Japanese	24[a]	970 ± 212	2480 ± 586
Capsule			38[b]	802 ± 277	2040 ± 648
		Caucasian	27[c]	450 ± 156	1210 ± 414
TAB-A	50	Japanese	23[a]	2070 ± 552	5170 ± 1520
Capsule			36[b]	1550 ± 442	4200 ± 1490
		Caucasian	84[d]	825 ± 302	2350 ± 902

a, Study ONO-2370-01; b, pooled data from Studies ONO-2370-01 and BIA-91067-126;
c, Study BIA-91067-119; d, pooled data from Studies BIA-91067-119, BIA-91067-120, and BIA-91067-125

PMDA's view:

Based on the submitted data, the PK of opicapone may be affected by regional differences in dietary habits. Nevertheless, opicapone was administered under fasted conditions in all the Japanese and foreign clinical studies that investigated differences in the PK of opicapone between Japanese and non-Japanese populations, the reason for the differences between the populations are not necessarily conclusive. However, given that regional differences are consistently noted for the PK of opicapone, if the same dose level of opicapone is administered under conditions similar to those used in Study 302, the foreign study used for bridging, and Japanese Study 02, the bridging study, it is possible that opicapone exposure in Japanese population be approximately 2-fold the exposure in Caucasians. Therefore, the appropriateness of developmental strategies with the bridging approach and the validity of the bridging should be verified taking account of the difference in exposure [see Section "7.R.2 Appropriateness of the developmental strategy with a bridging approach and the validity of bridging"].

6.R.2 Food effect and dose timing of opicapone

The applicant's explanation about timings of opicapone dose and meals:

The results of the food effect study (Study ONO-2370-03) showed that C_{max} and AUC of opicapone decreased following the dose of opicapone under fed conditions as compared to that under fasted conditions. The formulation used in Study ONO-2370-03 (TAB-B 50 mg) is not identical to the to-be-marketed formulation (TAB-B 25 mg). However, in Study ONO-2370-01, which used TAB-A shown to be bioequivalent with TAB-B, the PK parameters of opicapone did not differ significantly between the products of different strengths [see Section "6.1 Summary of biopharmaceutic studies and associated analytical methods"]. Given these results, it is unlikely that the difference between the to-be-marketed formulation (TAB-B 25 mg) and TAB-B 50 mg will affect the PK of opicapone, and the food effect on the PK of opicapone for the to-be-marketed formulation is able to be evaluated based on the results of Study ONO-2370-03.

Accordingly, although blood opicapone concentration was affected by food, the proposed regimen of opicapone specifies bedtime dosing, and that is consistent with the regimens of the studies conducted in patients with PD to assess the efficacy and safety of opicapone, namely, the Japanese phase II study (Study 02) and foreign phase III studies (Foreign Studies 301 and 302). Given this, opicapone is unlikely to be taken soon before or after meal. Meanwhile, Study 302 required opicapone to be administered at a ≥1 hour-interval before or after meal, and Foreign Study 301 did not require specific timing of opicapone dose and meals. This difference between the studies did not cause clear differences in efficacy or safety at 25 or 50 mg [see Section "7.3 Phase III studies"]. In addition, in the foreign phase I study (Study BIA-91067-128) conducted to assess food effect on the PK and pharmacodynamic action (S-COMT inhibition) following the multiple oral doses of opicapone 50 mg, C_{max} and AUC of opicapone decreased to approximately 0.4-fold and 0.7-fold, respectively, under fed conditions as compared with fasted conditions as in Study ONO-2370-03. However, opicapone's inhibitory effect against S-COMT activity was not significantly affected by meals.

Based on the above, it may not be necessary to specify the dose timing of opicapone relative to meal in the "Dosage and Administration" section. Nevertheless, the PK of opicapone is affected by food, and given this, the "Precautions Concerning Dosage and Administration" section of the package inert should highlight that opicapone should be administered ≥1 hour before or after meal

PMDA's view:
Exposure to opicapone is shown to decrease under fed conditions as compared with that under fasted conditions. However, the submitted data indicate no clear influence of different dose and meal timings on the pharmacodynamic action of opicapone. In addition to this result, given that it is appropriate to specify bedtime dosing, the dose and meal timings need not be specified in the dosage regimen of opicapone. However, Japanese Study 02 required subjects to take opicapone ≥1 hour before or after meal due to possible food effect on the PK of opicapone and demonstrated the efficacy and safety of opicapone in Japanese patients with PD. Therefore, it is appropriate to advice that opicapone be taken ≥1 hour before or after meal in the "Precautions Concerning Dosage and Administration" section.

The adequacy of elements in the dosage regimen of opicapone other than dose and meal timings are discussed in Section "7.R.6 Dosage and administration" taking also into account the efficacy and safety data from the Japanese phase II study (Japanese Study 02) and foreign phase III studies (Foreign Studies 301 and 302).

6.R.3 Use of opicapone in patients with hepatic impairment

The applicant's explanation about the use of opicapone in patients with hepatic impairment:
In Study BIA-91067-106, a foreign phase I study in which the effect of hepatic impairment on the PK of opicapone was investigated, both C_{max} and AUC of opicapone showed approximately 2-fold increases in subjects with moderate hepatic impairment (Child-Pugh B) as compared with those of subjects with normal hepatic function. Given that multiple oral doses of opicapone 50 mg, which is twice the proposed dose, was

demonstrated to be well tolerated in patients with PD [see Section "7.2 Japanese phase II study"], the dose of opicapone needs not be reduced for patients with PD having moderate or milder hepatic impairment. However, plasma opicapone concentration may increase in such patients as compared to those in patients with normal hepatic function. Therefore, careful use of opicapone will be advised via the package insert. At the same time, given that opicapone has never been used in patients with severe hepatic impairment (Child-Pugh C) and that liver metabolism is the major elimination pathway of opicapone, the possibility cannot be ruled out that plasma opicapone concentration may become higher in patients with severe hepatic impairment than in those with moderate hepatic impairment. Therefore, the use of opicapone should be contraindicated in patients with severe hepatic impairment.

PMDA's view:

Although the results of Study BIA-91067-106 indicated increased plasma opicapone concentration in patients with moderate hepatic impairment, in light of the degree of increase in the plasma opicapone concentration, etc. observed in this patient population, it is reasonable not to require dose adjustment but to advise careful use of opicapone for patients with mild or moderate hepatic impairment. Although the degree of increase in plasma opicapone concentration in patients with severe hepatic impairment is not clearly known, opicapone is mainly eliminated by liver metabolism, and thus the possibility cannot be ruled out that plasma opicapone concentrations could become higher in patients with severe hepatic impairment than in those with moderate hepatic impairment, as explained by the applicant. Furthermore, opicapone has never been used in patients with severe hepatic impairment. Accordingly, it is appropriate to contraindicate opicapone in patients with severe hepatic impairment as the applicant's proposal.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the main clinical result data from 8 studies listed in Table 27 [see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA" for the details of PK].

Table 27. Outline of main clinical studies

Data	Location	Study ID	Phase	Study population	Number of participants enrolled	Summary of dosage regimen	Main endpoint
Evaluation data	Japan	ONO-2370-03	I	Healthy adults	12	A single oral dose of opicapone 50 mg under fasted or fed conditions	PK Safety
	Foreign	BIA-91067-128	I	Healthy adults	28	Oral doses of opicapone 50 mg once daily for 12 days	PK Safety
	Japan	ONO-2370-01	I	Healthy adults	Part I, 48 Part II, 80	Part I: A single oral dose of opicapone 25 or 50 mg tablet or capsule Part II: Oral doses of opicapone 5, 10, 25, or 50 mg tablets a once daily for 11 days, and oral levodopa/carbidopa 100/10 mg 3 times daily on the day before the first dose of opicapone and the day following the last dose of opicapone	PK
	Foreign	BIA-91067-126	I	Healthy adults	105 (54 Japanese, 51 Caucasians)	Oral doses of placebo, opicapone 5, 25, or 50 mg once daily for 10 days	PK Safety
	Foreign	BIA-91067-124	I	Healthy adults	80	Days 1-11: Oral placebo, opicapone 25, 50, or 75 mg once daily Day 12: Oral entacapone 200 mg or placebo + levodopa/carbidopa 100/25 mg 3 times daily	PK Safety
	Japan	ONO-2370-02[a]	II	Patients with PD experiencing wearing-off who have been treated with levodopa/DCI	Double-blind period, 437 Open-label period, 391	Double-blind period: Oral placebo, opicapone 25 or 50 mg once daily at bedtime[c] Open-label period: Oral opicapone 50 mg once daily at bedtime[c]	Efficacy Safety
	Foreign	BIA-91067-301	III	Patients with PD with end-of-dose motor fluctuations	Double-blind period, 600 Open-label period, 495	Double-blind period: Oral placebo, opicapone 5, 25, or 50 mg once daily at bedtime,[c] and oral placebo or entacapone 200 mg + levodopa/DCI 3-8 times daily Open-label period: Oral opicapone 5, 25, or 50 mg (25 mg in the first week, and adjusted according to the subject's clinical response in subsequent weeks) once daily at bedtime[c]	Efficacy Safety
	Foreign	BIA-91067-302[b]	III	Patients with PD with end-of-dose motor fluctuations	Double-blind period, 427 Open-label period, 367	Double-blind period: Oral placebo, opicapone 25 or 50 mg once daily at bedtime[c] Open-label period: Oral opicapone 25 or 50 mg (25 mg in the first week and adjusted according to the subject's clinical response) once daily at bedtime[c]	Efficacy Safety

a, the bridging study; b, the study used for bridging; c, ≥1 hour after administration of the last daily dose of levodopa/DCI.

7.1 Phase I studies

7.1.1 Food effect study (Study ONO-2370-03, CTD 5.3.1.1-1 [[redacted] to [redacted] 2017])

A randomized, open-label, 2-treatment, 2-period crossover study to assess the food effect of on the PK of opicapone was conducted in Japanese healthy adults at 1 site in Japan. A single oral dose of opicapone 50 mg was administered under fasted or fed conditions (washout period, 7 days; target sample size, 12).

The enrolled 12 subjects received the study drug, and all of them were included in the safety analysis set. No treatment discontinuation occurred.

No adverse events occurred.

7.1.2 Single-dose and multiple-dose Japanese studies (Study ONO-2370-01, CTD 5.3.1.2-1 [August 2014 to [redacted] 2015])

A study consisting of 2 parts, a randomized open-label 2-treatment, 2-period crossover part (Part I) and an open-label, 3-period crossover part (Part II), was conducted at 1 site in Japan in Japanese healthy adults to assess bioequivalence of 2 dosage forms of opicapone, tablets and capsules (Part I), and the effects of opicapone on the PK of levodopa (Part II) (washout period, ≥28 days [Part I]; target sample size, 48 [Part I], and 80 [Part II]).

In Part I, a single dose of opicapone 25 or 50 mg tablet or capsule was administered orally under fasted conditions. In Part II, opicapone 5, 10, 25, or 50 mg tablets were administered orally once daily for 11 days under fasted conditions at bedtime (Period 2), and levodopa/carbidopa 100/10 mg preparation was administered orally 3 times daily on the day before the first dose of opicapone (Period 1) and the day following the last dose of opicapone (Period 3).

In Part I, 48 enrolled subjects received the study drug, and all of them were included in the safety analysis set. In Part II, 80 enrolled subjects received the study drug or levodopa/carbidopa preparation, and all of them were included in the safety analysis set. Treatment discontinuation occurred in 1 subject in Part I (opicapone 50 mg group; discontinued during the washout period at the discretion of the principal [sub] investigator), and in 2 subjects in Part II (1 subject in the opicapone 10 mg group discontinued at the request of the subject after administration of the first dose of levodopa/carbidopa in Period 1; 1 subject in the opicapone 50 mg group discontinued due to adverse events on Day 7 [during Period 2]).

In Part I, the incidence of adverse events was 0% (0 of 24 subjects) in patients dosed with a opicapone 25-mg tablet and 0% (0 of 24 subjects) in those dosed with a 25-mg capsule; and 0% (0 of 23 subjects) in patients dosed with a opicapone 50-mg tablet and 4.2% (1 of 24 subjects) in those dosed with a opicapone 50-mg capsule (blood creatine phosphokinase [CK] increased). No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

Table 28 shows the overall incidence of adverse events and the major adverse events in Part II. No deaths or serious adverse events occurred. An adverse event led to treatment discontinuation in 1 subject (opicapone 50 mg during Period 2, enteritis infectious), and a causal relationship to the study drug was ruled out.

Table 28. Incidences of adverse events in Part II (safety analysis set)

	Opicapone 5 mg			Opicapone 10 mg		
	Period 1 (n = 20)	Period 2 (n = 20)	Period 3 (n = 20)	Period 1 (n = 20)	Period 2 (n = 19)	Period 3 (n = 19)
Adverse events	5.0 (1)	0 (0)	5.0 (1)	0 (0)	5.3 (1)	0 (0)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

% (number of subjects)
Periods 1 and 3, dosing of levodopa/carbidopa preparation; Period 2, opicapone dosing

	Opicapone 25 mg			Opicapone 50 mg		
	Period 1 (n = 20)	Period 2 (n = 20)	Period 3 (n = 20)	Period 1 (n = 20)	Period 2 (n = 20)	Period 3 (n = 19)
Adverse events	0 (0)	0 (0)	15.0 (3)	0 (0)	10.0 (2)	26.3 (5)
Nausea	0 (0)	0 (0)	15.0 (3)	0 (0)	0 (0)	26.3 (5)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	15.8 (3)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10.5 (2)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	5.0 (1)	0 (0)

% (number of subjects)
Periods 1 and 3, dosing of levodopa/carbidopa preparation; Period 2, opicapone dosing

7.1.3 Study to compare PK parameters (Study BIA-91067-126, CTD 5.3.3.3-4 [[redacted] 2011 to [redacted] 2012])

A randomized, double-blind study was conducted at 1 overseas site to evaluate the PK of opicapone in Japanese or non-Japanese healthy adults receiving oral placebo or opicapone 5, 25, or 50 mg once daily for10 days (target sample size, ≤38 subjects per group; 19 each of Japanese and non-Japanese).

The study drugs were administered to 105 enrolled subjects (29 subjects [14 Japanese and 15 non-Japanese] in the placebo group, 27 subjects [14 and 13] in the opicapone 5 mg group, 26 subjects [14 and 12] in the 25 mg group, 23 subjects [12 and 11] in the 50 mg group), and all 105 subjects were included in the safety analysis set. Treatment discontinuation occurred in 2 subjects (1 Japanese subject in the opicapone 25 mg group discontinued after the Day 3 dose due to consent withdrawal; 1 non-Japanese subject in the opicapone 5 mg group discontinued after the Day 10 dose due to consent withdrawal).

Table 29 shows the overall incidence of adverse events and the main adverse events.

Table 29. Incidences of adverse events (safety analysis set)

	Japanese				Non-Japanese			
	Placebo (n = 14)	Opicapone			Placebo (n = 15)	Opicapone		
		5 mg (n = 14)	25 mg (n = 14)	50 mg (n = 12)		5 mg (n = 13)	25 mg (n = 12)	50 mg (n = 11)
Adverse events	35.7 (5)	21.4 (3)	42.9 (6)	50.0 (6)	53.3 (8)	53.8 (7)	41.7 (5)	54.5 (6)
Vessel puncture site haematoma	14.3 (2)	7.1 (1)	14.3 (2)	25.0 (3)	13.3 (2)	30.8 (4)	25.0 (3)	0 (0)
Headache	14.3 (2)	14.3 (2)	7.1 (1)	8.3 (1)	6.7 (1)	0 (0)	0 (0)	9.1 (1)
Tension headache	0 (0)	0 (0)	0 (0)	16.7 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Contusion	0 (0)	7.1 (1)	0 (0)	0 (0)	13.3 (2)	7.7 (1)	0 (0)	0 (0)

% (number of subjects)

No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

7.1.4 Foreign multiple-dose study (1) (Study BIA-91067-128, CTD 5.3.1.1-3 [November 2014 to January 2015])

An open-label study was conducted at 1 overseas site in non-Japanese healthy adults (target sample size, 28 subjects) to investigate the food effect on the PK of opicapone following multiple oral doses of opicapone 50-mg capsule administered for 12 days under fasted conditions (after a meal on only Day 10).

The study drug was administered to 28 enrolled subjects and all of them were included in the safety analysis set. No treatment discontinuation occurred.

The incidence of adverse events was 35.7% (10 of 28 subjects), and the major events were headache (5), abdominal pain (2), and fatigue (2).

No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

7.1.5 Foreign multiple-dose study (2) (Study BIA-91067-124, CTD 5.3.3.4-13 [September 2011 to January 2012])

A randomized, double-blind study was conducted at 1 overseas study site in non-Japanese healthy adults (target sample size, 80 subjects) to investigate the effect of opicapone on the PK of levodopa.

As summarized in Table 30, placebo or opicapone 25, 50, or 75 mg was administered orally once daily for 11 days (Days 1-11). On Day 12, placebo or entacapone 200 mg + levodopa/carbidopa 100/25 mg preparation were administered orally 3 times daily.

Table 30. Dosage regimen

		Placebo group	Opicapone group	Entacapone group
Days 1-11	Once daily	Placebo	Opicapone 25, 50, or 75 mg	Placebo
Day 12	3 times daily	Placebo + levodopa/carbidopa 100/25 mg		Entacapone 200 mg + levodopa/carbidopa 100/25 mg

The study dugs were administered to 80 enrolled subjects, and all of them were included in the safety analysis set. Treatment discontinuation occurred in 1 subject (opicapone 25 mg group; discontinued after the Day 10 dose due to consent withdrawal).

The incidence of adverse events for each group was as follows: 68.8% (11 of 16 subjects) in the placebo group, 31.3% (5 of 16 subjects) in the opicapone 25 mg group, 50.0% (8 of 16 subjects) in the opicapone 50 mg group, 50.0% (8 of 16 subjects) in the opicapone 75 mg group, and 56.3% (9 of 16 subjects) in the entacapone group. The major adverse events are shown in Table 31.

Table 31. Adverse events with an incidence of ≥10% in any group (safety analysis set)

	Placebo (n = 16)	Opicapone 25 mg (n = 16)	Opicapone 50 mg (n = 16)	Opicapone 75 mg (n = 16)	Entacapone (n = 16)
Nausea	25.0 (4)	18.8 (3)	50.0 (8)	50.0 (8)	31.3 (5)
Vomiting	6.3 (1)	18.8 (3)	12.5 (2)	18.8 (3)	6.3 (1)
Headache	12.5 (2)	12.5 (2)	12.5 (2)	6.3 (1)	31.3 (5)
Dizziness	12.5 (2)	6.3 (1)	6.3 (1)	0 (0)	0 (0)
Hot flush	6.3 (1)	0 (0)	18.8 (3)	12.5 (2)	0 (0)
Diarrhoea	0 (0)	0 (0)	12.5 (2)	0 (0)	0 (0)

% (number of subjects)

No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

7.2 Japanese phase II study (Study ONO-2370-02, bridging study, CTD 5.3.5.1-1 [January 2016 to [redacted] 2018])

Japanese Study 02 was conducted in Japanese patients with PD experiencing wearing-off who had been treated with levodopa/DCI to investigate the efficacy and safety of opicapone. The study consisted of a randomized, double-blind period (double-blind period) and an open-label uncontrolled period (open-label period) and was conducted at 72 sites in Japan (target sample size, 399 [133/group]).

The double-blind period consisted of the treatment phase (a 2 to 3-week levodopa dose adjustment period and a 12-week levodopa dose maintenance period) and the transition phase (≤4 weeks). Placebo or opicapone 25, or 50 mg was administered orally once daily at bedtime, ≥1 hour after the last daily dose of levodopa/DCI. The double-blind period was followed by a 52-week open-label period, in which opicapone 50 mg was administered orally once daily as was during the double-blind period. From 4 weeks before the start of screening through the study period, the use of entacapone or apomorphine hydrochloride hydrate was prohibited. The dosage regimen of levodopa/DCI or any other anti-PD drug taken was to remain unchanged during the double-blind period (only dose modification of levodopa/DCI in the levodopa dose adjustment period was allowed). In the open-label period, the dose was allowed be modified.

Eligible subjects were patients aged ≥30 and ≤83 years meeting the following main inclusion criteria:

- Having idiopathic PD diagnosed ≥3 years ago according to the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria, with a severity of Stage I to III (modified Hoehn & Yahr staging) during ON-time at the start of screening
- Receiving levodopa/DCI continuously for ≥1 year and being considered to have a response to the treatment by the principal (sub) investigator
- Receiving 3 to 8 daily doses of levodopa/DCI at the start of screening
- Showing a sign of wearing-off phenomenon since ≥4 weeks before screening, with a total daily OFF-time of ≥1.5 hours while awake (excluding the OFF-time after wake-up and before responding to the first dose of levodopa/DCI), while receiving an anti-PD therapy that is considered optimum by the principal (sub) investigator

(a) Double-blind period (excluding the transition phase)

A total of 437 subjects were randomized to placebo (147), opicapone 25 mg (145), or opicapone 50 mg (145) and received the study drugs. All 437 subjects were included in the safety analysis set. A total of 2 subjects in the opicapone 25 mg group had no primary efficacy endpoint assessment and were excluded from the full analysis set (FAS), which thus included the remaining 435 subjects (147, 143, and 145) and was subjected to the primary efficacy analysis. Treatment discontinuation occurred in 36 subjects (6, 12, and 18), and the reasons for discontinuation were "request of the subject" in 19 subjects (3, 6, and 10), and "adverse events" in 17 subjects (3, 6, and 8).

Table 32 shows the change from baseline in OFF-time[3)] at the end of the treatment phase (12 weeks after the completion of the levodopa dose adjustment period), the primary endpoint for the study. Both opicapone 25 mg ($P = 0.0145$) and 50 mg ($P = 0.0392$) demonstrated a significant difference from placebo.

Table 32. Change from baseline in OFF-time (minutes) at the end of the treatment phase (FAS, last observation carried forward [LOCF])

	Placebo	Opicapone 25 mg	Opicapone 50 mg
Baseline Mean ± standard deviation	n = 147 375.31 ± 153.90	n = 143 353.04 ± 137.33	n = 145 361.41 ± 140.40
At the end of treatment phase Mean ± standard deviation	n = 139 343.09 ± 183.85	n = 132 281.97 ± 177.02	n = 127 294.84 ± 169.58
Change from baseline Least squares mean ± standard error[a]	−25.04 ± 12.77	−69.72 ± 12.94	−62.51 ± 12.84
Difference from placebo in change Least squares mean [95% CI][a]	—	−44.68 [−80.45, −8.91]	−37.47 [−73.07, −1.87]

a, analyses of covariance (ANCOVA) using treatment group as a factor and baseline OFF-time as a covariate.
First, the opicapone 50 mg group was compared with placebo group. If a significant difference was shown, then the opicapone 25 mg group was compared with placebo group (with a two-sided significance level of 5%).

The incidence of adverse events was 48.3% (71 of 147 subjects) in the placebo group, 60.0% (87 of 145 subjects) in the opicapone 25 mg group, and 54.5% (79 of 145 subjects) in the 50 mg group. The major adverse events are listed in Table 33.

[3)] The average of total daily OFF-time (assessed at 30-minute intervals) in the 3 days before each visit according to the subject's diary. If a value for 1 of the 3 days before visit was missing, the average was calculated based on the values of the remaining 2 days, and if values for 2 days were missing, the value for the remaining day was used.

Table 33. Adverse events with an incidence of ≥3% in any group (safety analysis set)

	Placebo (n = 147)	Opicapone 25 mg (n = 145)	Opicapone 50 mg (n = 145)
Dyskinesia	2.7 (4)	9.0 (13)	12.4 (18)
Nasopharyngitis	8.2 (12)	7.6 (11)	3.4 (5)
Constipation	2.0 (3)	4.8 (7)	3.4 (5)
Nausea	1.4 (2)	4.1 (6)	4.8 (7)
Contusion	6.8 (10)	3.4 (5)	4.1 (6)
Fall	0.7 (1)	2.8 (4)	3.4 (5)
Blood urine present	3.4 (5)	2.1 (3)	0 (0)
Thirst	0 (0)	0.7 (1)	3.4 (5)
Back pain	3.4 (5)	0 (0)	0.7 (1)

% (number of subjects)

No deaths occurred. Serious adverse events occurred in 2 subjects in the placebo group (humerus fracture/radius fracture and contusion), 8 subjects in the opicapone 25 mg group (bile duct stone, pneumonia, femur fracture, subdural haematoma/peripheral arterial occlusive disease, upper limb fracture, osteonecrosis, gastric cancer stage I, and syncope/Parkinson's disease), and 3 subjects in the opicapone 50 mg group (cellulitis/haematoma, dyskinesia, and orthostatic hypotension). A causal relationship to the study drug could not be ruled out for pneumonia and syncope in the opicapone 25 mg group, dyskinesia and orthostatic hypotension in the opicapone 50 mg group.

Adverse events led to treatment discontinuation of the study drug in 3 subjects in the placebo group (malaise, gastric adenoma, and dyskinesia), 6 subjects in the opicapone 25 mg group (subdural haematoma, upper limb fracture, osteonecrosis, dyskinesia, hallucination, and hallucination/hallucination visual/pollakiuria/flushing), and 9 subjects in the opicapone 50 mg group (spinal stenosis, dyskinesia, delirium/hallucination visual, hallucination, hallucination visual/intentional self-injury, dermatitis contact, haemorrhage subcutaneous, rash, and blood pressure fluctuation).

(b) Transition phase

No deaths occurred. Serious adverse events occurred in 2 subjects in the placebo group (spinal compression fracture and anaemia) and 1 subject in the opicapone 25 mg group (radius fracture), and a causal relationship to the study drug was ruled out for all these events.

An adverse event led to treatment discontinuation in 1 subject in the placebo group (spinal compression fracture).

(c) Open-label period

A total of 391 subjects entered the open-label period and received the study drug. All the subjects were included in the safety analysis set. Of the 391, except 4 subjects who had been not assessed for the primary efficacy endpoint, 387 subjects were included in the FAS and were subjected to the primary efficacy analysis set. Treatment discontinuation occurred in 75 subjects, and the major reasons for discontinuation were "request of the subject" in 38 subjects and "adverse events" in 26 subjects.

Table 34 shows the change from baseline of the double-blind period in OFF-time.

Table 34. Change in OFF-time (minutes) (FAS)

	Opicapone 50 mg		
	N	Absolute time	Change[a]
Baseline in the double-blind period	387	363.62 ± 146.42	—
Week 24 in the open-label period	351	261.85 ± 169.51	−102.99 ± 162.19
Week 52 in the open-label period	315	261.92 ± 177.88	−101.89 ± 170.84

Mean ± standard deviation
a, change from baseline of the double-blind period

The incidence of adverse events was 86.4% (338 of 391 subjects), and the main adverse events are listed in Table 35.

Table 35. Adverse events with an incidence of ≥5% (safety analysis set)

	Opicapone 50 mg (n = 391)
Nasopharyngitis	16.9 (66)
Dyskinesia	12.0 (47)
Contusion	9.0 (35)
Constipation	7.2 (28)
Fall	6.4 (25)
Back pain	5.9 (23)
Weight decreased	5.4 (21)

% (number of subjects)

A death occurred in 1 subject (subdural haematoma), for which a causal relationship to the study drug was ruled out.

Other serious adverse events occurred in 56 subjects, and those that occurred in >1 subjects were Parkinson's disease (7), pneumonia aspiration (4), and pneumonia (3). Among the serious adverse events, a causal relationship to the study drug could not be ruled out for the following events in 1 subject each: atrioventricular block complete, ileus, volvulus, large intestine polyp/prostate cancer, decreased activity/pneumonia, pyrexia, breast cancer, dyskinesia, Parkinson's disease, and hallucination visual.

Adverse events led to treatment discontinuation of the study drug in 23 subjects, and those that occurred in more than 1 subject were Parkinson's disease (4) and hallucination (2).

7.3 Phase III studies

7.3.1 Foreign phase III study (1) (Study BIA-91067-301, CTD 5.3.5.1-2 and 3 [March 2011 to [redacted] 20[redacted]])

Study BIA-91067-301 was conducted in non-Japanese patients with PD experiencing wearing-off who had been treated with levodopa/DCI to investigate the efficacy and safety of opicapone. The study consisted of a

randomized, double-blind period (double-blind period) and an open-label uncontrolled period (open-label period) and conducted 106 overseas sites (target sample size, 550 [110 per group]).

The double-blind period consisted of the levodopa dose adjustment period (2-3 weeks) and the levodopa dose maintenance period (12 weeks). As summarized in Table 36, placebo, opicapone 5, 25, or 50 mg was administered orally once daily at bedtime (≥1 hour after the last daily dose of levodopa/DCI), and placebo or entacapone 200 mg was administered orally 3 to 8 times daily, simultaneously with each dose of levodopa/DCI.

Table 36. Dosage regimen of the study drugs in the double-blind period

		Placebo group	Opicapone group	Entacapone group
Double-blind period	Bedtime[a]	Placebo	Opicapone 5, 25, or 50 mg	Placebo
	Daytime[b]	Placebo	Placebo	Entacapone 200 mg

a, ≥1 hour after the last daily dose of levodopa/DCI
b, simultaneously with each dose of levodopa/DCI (3-8 times daily)

The double-blind period was followed by the 52-week open-label period. In the first week of the open-label period, opicapone 25 mg was administered once daily at bedtime (≥1 hour after the last daily dose of levodopa/DCI). From Weeks 2 to 46, the daily dose of opicapone was able to be adjusted according to the criteria shown in Table 37. During the subsequent 6 weeks, however, the dosage regimen of opicapone was to remain unchanged.

Table 37. Dose adjustment criteria for opicapone in the open-label period

	Opicapone group
Open-label period Week 2-46	If wearing-off was not controlled adequately in a subject showing tolerance to the treatment, dose increase of opicapone to 50 mg was allowed at the principal (sub) investigator's discretion. In case of an unacceptable dopaminergic adverse events: Only the daily dose of levodopa/DCI was adjusted. If not effective enough, the opicapone dose was reduced according to the steps below. • For subjects receiving opicapone 50 mg, reduce to 25 mg, and further reduce to 5 mg if necessary. • For subjects receiving opicapone 25 mg, reduce to 5 mg. In case of a non-dopaminergic adverse events: The dose of opicapone was to be adjusted according to the steps for the case of dopaminergic adverse events, independent of the levodopa/DCI dose adjustment.

Subjects were prohibited from receiving apomorphine hydrochloride hydrate and monoamine oxidase (MAO) inhibitors (except oral selegiline hydrochloride ≤10 mg/day [oral] or 1.25 mg/day [buccal] or rasagiline mesilate ≤1 mg/day [as rasagiline]) from 4 weeks before and during the study. Subjects received levodopa/DCI according to the dosage regimen presented in Table 38. The dosage regimen for other anti-PD drugs was to remain unchanged.

Table 38. Dosage regimen of levodopa/DCI

Prior to study	The dosage regimen was to remain changed from 4 weeks prior to study.
Double-blind period	Levodopa dose adjustment period (2-3 weeks) The daily dose of levodopa/DCI was allowed to be reduced at the discretion of the principal [sub] investigator according to the subject's response to the study drug. Change in the number of dose per day was not allowed. The reduced dose was allowed to be reversed to the baseline daily dose at the discretion of the principal (sub) investigator. Levodopa dose maintenance period (12 weeks) No change in the dosage regimen
Open-label period	Levodopa dose adjustment period (46 weeks) The dose was allowed to be adjusted according to the subject's response and tolerability to the study drug at the discretion of the principal (sub) investigator. Levodopa dose maintenance period (6 weeks) No change in the dosage regimen

Eligible subjects were patients aged ≥30 and ≤83 years meeting the following main inclusion criteria:

- Having idiopathic PD diagnosed ≥3 years ago according to the UKPDS Brain Bank Clinical Diagnostic Criteria, with a severity of Stage I to III (modified Hoehn & Yahr staging) during ON-time at the start of screening
- Receiving levodopa/DCI continuously for ≥1 year and being considered to have a response to the treatment by the principal (sub) investigator
- Receiving 3 to 8 daily doses of levodopa/DCI at the start of screening
- Showing a sign of wearing-off phenomenon since ≥4 weeks before the start of the study, with a total daily OFF-time of ≥1.5 hours while awake (excluding the OFF-time after wake-up and before responding to the first dose of levodopa/DCI), while receiving an anti-PD therapy that is considered optimum by the principal (sub) investigator

(a) Double-blind period

A total of 600 subjects were randomized to placebo (121), opicapone 5 mg (122), opicapone 25 mg (119), opicapone 50 mg (116), and entacapone (122)). One subject assigned to opicapone 50 mg was excluded, and the remaining 599 subjects received the study drug (121, 122, 119, 115, and 122) and were included in the safety analysis set. Except 9 subjects were not assessed for primary efficacy endpoint (1, 3, 3, 0, and 2), 590 subjects (120, 119, 116, 115, and 120, respectively) were included in the FAS. Of the FAS, 537 subjects with no major protocol deviations (112, 110, 105, 106, and 104) were included in the per protocol set (PPS). The FAS was the primary analysis set to assess superiority over placebo, and the PPS was the primary analysis set to assess non-inferiority to entacapone. Treatment discontinuation occurred in 58 subjects (11, 12, 11, 9, and 15), and the major reasons for discontinuation were "adverse events" in 36 subjects (8, 7, 8, 5, and 8) and "consent withdrawal" in 21 subjects (4, 3, 4, 4, and 6).

Table 39 shows the change from baseline in OFF-time[4)] at the end of the double-blind period (12 weeks after the completion of the levodopa dose adjustment period), the primary endpoint for the study. The results

[4)] The average of total daily OFF-time (assessed at 30-minute intervals) in the 3 days before each visit according to the subject's diary

demonstrated the superiority of opicapone 50 mg over placebo, and the non-inferiority of opicapone 50 mg to entacapone (non-inferiority margin was 30 minutes[5)]).

Table 39. Change from baseline in OFF-time (minutes) at the end of the double-blind period (LOCF)

FAS					
	Placebo (n = 120)	Opicapone 5 mg (n = 119)	Opicapone 25 mg (n = 116)	Opicapone 50 mg (n = 115)	Entacapone (n = 120)
Baseline Mean ± standard deviation	370.1 ± 106.72	403.2 ± 128.10	411.2 ± 132.29	372.2 ± 106.95	387.6 ± 130.47
At the end of treatment phase Mean ± standard deviation	325.3 ± 166.17	307.2 ± 153.88	316.6 ± 162.21	265.4 ± 142.54	294.1 ± 165.64
Change from baseline Least squares mean ± standard error[a]	−56.0 ± 13.37	−91.3 ± 13.46	−85.9 ± 13.69	−116.8 ± 13.97	−96.3 ± 13.40
Difference from placebo in change Least squares mean [95% CI][a]	—	−35.2 [−71.4, 0.9]	−29.9 [−66.3, 6.5]	−60.8 [−97.2, −24.4]	—
Adjusted *P*-value[b] (superiority to placebo)	—	0.0558	0.0796	0.0015	—
PPS					
	Placebo (n = 112)	Opicapone 5 mg (n = 110)	Opicapone 25 mg (n = 105)	Opicapone 50 mg (n = 106)	Entacapone (n = 104)
Baseline Mean ± standard deviation	374.0 ± 105.45	406.1 ± 118.90	413.6 ± 126.26	367.0 ± 106.20	394.7 ± 110.67
At the end of treatment phase Mean ± standard deviation	328.3 ± 163.48	307.1 ± 155.36	312.2 ± 154.89	263.6 ± 140.77	304.4 ± 155.66
Change from baseline Least squares mean ± standard error[a]	−56.2 ± 13.63	−92.6 ± 13.75	−93.8 ± 14.17	−115.6 ± 14.33	−89.4 ± 14.31
Difference from entacapone in change Least squares mean [95% CI][a]	—	−3.2 [−40.4, 33.9]	−4.4 [−42.0, 33.2]	−26.2 [−63.8, 11.4]	—
Adjusted *P*-value[b] (non-inferiority to entacapone)	—	—	—	0.00518	—

a, ANCOVA using treatment group and region as factors, and baseline OFF-time as a covariate

b, An overall one-sided significance level of 2.5% was used. To adjust for multiplicity of testing for the superiority of each opicapone group to placebo and the non-inferiority of each opicapone group to entacapone, a sequential gatekeeping procedure (*Biom J*. 2011, 53,894-913), in which the significance level was split by the Bonferroni method, was used for the comparison of the 3 opicapone groups and placebo.

The incidence of adverse events was 49.6% (60 of 121 subjects) in the placebo group, 51.6% (63 of 122 subjects) in the opicapone 5 mg group, 54.6% (65 of 119 subjects) in the 25 mg group, 53.9% (62 of 115 subjects) in the 50 mg group, and 56.6% (69 of 122 subjects) in the entacapone group. The major adverse events are listed in Table 40.

Table 40. Adverse events with an incidence of ≥5% in any group (safety analysis set)

	Placebo (n = 121)	Opicapone 5 mg (n = 122)	Opicapone 25 mg (n = 119)	Opicapone 50 mg (n = 115)	Entacapone (n = 122)
Dyskinesia	4.1 (5)	13.9 (17)	7.6 (9)	15.7 (18)	8.2 (10)
Insomnia	0.8 (1)	1.6 (2)	5.9 (7)	6.1 (7)	5.7 (7)
Dizziness	0.8 (1)	1.6 (2)	5.0 (6)	2.6 (3)	4.1 (5)
Hallucination	0.8 (1)	0.8 (1)	5.0 (6)	0.9 (1)	0.8 (1)
Nausea	1.7 (2)	1.6 (2)	2.5 (3)	2.6 (3)	6.6 (8)
Back pain	5.0 (6)	3.3 (4)	2.5 (3)	0 (0)	0.8 (1)
Constipation	2.5 (3)	3.3 (4)	0 (0)	6.1 (7)	4.1 (5)

% (number of subjects)

[5)] The margin was specified based on data from literature, i.e., the difference between the entacapone and placebo groups being −0.8 hours indicated by the pooled analyses in phase III studies of entacapone as well as a presumed difference between the opicapone and placebo groups of approximately 60 minutes.

No deaths occurred. Serious adverse events occurred in 6 subjects in the placebo group (visual impairment, pancreatitis acute/gastritis/hepatitis acute/hypertension/duodenitis, near drowning/pneumonia aspiration, hepatic enzyme increased, back pain, and superficial spreading melanoma stage unspecified), 4 subjects in the opicapone 5 mg group (wrist fracture, hepatic enzyme increased, pain in extremity, and basal cell carcinoma), 1 subject in the 25 mg group (Bowen's disease), 4 subjects in the 50 mg group (coronary artery disease, constipation, inguinal hernia, and dyskinesia), and 9 subjects in the entacapone group (pulmonary embolism/angina unstable/cor pulmonale acute, cholelithiasis/cholecystitis infective, erysipelas, contusion/fall, diabetes mellitus/femur fracture/fall/orthostatic hypotension, benign ear neoplasm, syncope, urinary tract inflammation, and glaucoma). A causal relationship to the study drug could not be ruled out for pancreatitis acute/hepatitis acute, superficial spreading melanoma stage unspecified, visual impairment, and hepatic enzyme increased in the placebo group; basal cell carcinoma and hepatic enzyme increased in the opicapone 5 mg group; dyskinesia in the 50 mg group; and pulmonary embolism/angina unstable/cor pulmonale acute and syncope in the entacapone group.

Adverse events led to treatment discontinuation of the study drug in 8 subjects in the placebo group (diarrhoea, duodenitis/gastritis/pancreatitis acute/hepatitis acute/hypertension, salivary hypersecretion/hypotonia/motor dysfunction, drug effect decreased, hepatic enzyme increased, freezing phenomenon, headache, and tremor), 7 subjects in the opicapone 5 mg group (dyskinesia in 2 subjects; abdominal pain, dysphagia, hepatic enzyme increased, myalgia, and hallucination visual), 8 subjects in the 25 mg group (vomiting, muscle haemorrhage/sleep attacks/rash, muscular weakness, dizziness, hallucination, hallucination visual, insomnia, and hypertension), 5 subjects in the 50 mg group (palpitations, dyspepsia, taste abnormality, hallucination auditory, and hallucination visual), and 8 subjects in the entacapone group (angina unstable and diarrhoea in 2 subjects each; drug effect decreased/weight decreased/enuresis, gamma-glutamyltransferase increased, akinesia, syncope, and urinary tract inflammation).

(b) Open-label period

A total of 495 subjects entered the open-label period and received the study drug. All the subjects were included in the safety analysis set. Of the 495, except 1 subject who was not assessed for the primary efficacy endpoint, 494 subjects were included in the FAS and subjected to the primary efficacy analysis. Treatment discontinuation occurred in 63 subjects, and the major reasons for discontinuation were "adverse events" in 30 subjects and "at the request of the subject" in 29 subjects.

Table 41 shows the change from baseline in OFF-time of the double-blind period.

Table 41. Change in OFF-time (minutes) (FAS)

	Opicapone group		
	N	Absolute time	Change[a]
Baseline in the double-blind period	494	387.4 ± 116.99	—
Final evaluation in the open-label period	494	260.5 ± 151.44	−126.9 ± 149.13

Mean ± standard deviation
a, change from baseline of the double-blind period

The incidence of adverse events was 68.1% (337 of 495 subjects), and the main adverse events are listed in Table 42.

Table 42. Adverse events with an incidence of ≥3% (safety analysis set)

	Opicapone group (n = 495)
Dyskinesia	14.5 (72)
Drug effect decreased	12.1 (60)
Parkinson's disease	6.7 (33)
Back pain	4.6 (23)
Insomnia	4.6 (23)
Nasopharyngitis	3.2 (16)
Orthostatic hypotension	3.2 (16)
Tremor	3.2 (16)
Constipation	3.0 (15)

% (number of subjects)

Death occurred in 11 subjects (lung disorder, death, pneumonia, cardiovascular insufficiency, myocardial infarction, embolism, pulmonary embolism, metastases to spine, small cell lung cancer [stage unspecified], multi-organ failure, and sudden death). A causal relationship to the study drug was ruled out for all these events.

Serious adverse events (including deaths) occurred in 48 subjects, and those that occurred in >1 subjects were intestinal obstruction and cauda equina syndrome in 3 subjects each; atrial fibrillation, bronchitis, pneumonia, ankle fracture, basal cell carcinoma, malignant melanoma, sciatica, benign prostatic hyperplasia, and hypertension in 2 subjects each. Among the serious adverse events, a causal relationship to the study drug could not be ruled out for epilepsy/wrist fracture, aggression/dementia, malignant melanoma in situ, and malignant melanoma/jealous delusion in 1 subject each.

Adverse events led to treatment discontinuation of the study drug in 27 subjects. Among these events, dyskinesia was observed in >1 subjects (4).

7.3.2 Foreign phase III study (2) (Study BIA-91067-302, study used for bridging, CTD 5.3.5.1-4, 5 [March 2011 to [redacted] 20[redacted]])

Foreign Study 302 was conducted in non-Japanese patients with PD experiencing wearing-off while treated with levodopa/DCI to investigate the efficacy and safety of opicapone. The study consisted of a randomized, double-blind period (double-blind period) and an open-label uncontrolled period (open-label period) and conducted at 71 overseas sites (target sample size, 405 [135 subjects/group]).

The double-blind period consisted of the levodopa dose adjustment period (2-3 weeks) and the levodopa dose maintenance period (12 weeks). Placebo or opicapone 25 or 50 mg was administered orally once daily at bedtime, ≥1 hour after the last daily dose of levodopa/DCI. The double-blind period was followed by the 52-week open-label period. In the first week of the open-label period, opicapone 25 mg was administered once daily at bedtime (≥1 hour after the last daily dose of levodopa/DCI), and in Weeks 2 to 46, the daily dose of opicapone was able to be changed according to the criteria in Table 37. For the subsequent 6 weeks, however, the dosage regimen of opicapone was not allowed to be changed.

The use of apomorphine and MAO inhibitors (except selegiline hydrochloride ≤10 mg/day [oral] or ≤1.25 mg/day [buccal], or rasagiline mesilate ≤1 mg/day [as rasagiline]) was prohibited during the 4-week pre-study period and throughout the study period. Levodopa/DCI was administered according to the dosage regimen presented in Table 38. The dosage regimen for other anti-PD drugs was not allowed to be changed.

Eligible subjects were patients aged ≥30 and ≤83 years meeting the following main inclusion criteria:

- Having idiopathic PD diagnosed ≥3 years ago according to the UKPDS Brain Bank Clinical Diagnostic Criteria, with a severity of Stage I to III (modified Hoehn & Yahr staging) during ON-time at the start of screening
- Receiving levodopa/DCI continuously for ≥1 year and being considered to have a response to the treatment by the principal (sub) investigator
- Receiving 3 to 8 daily doses of levodopa/DCI at the start of screening
- Showing a sign of wearing-off phenomenon since ≥4 weeks before screening, with an total daily OFF-time of ≥1.5 hours while awake (excluding the OFF-time after wake-up and before responding to the first dose of levodopa/DCI), while receiving an anti-PD therapy that is considered optimum by the principal (sub) investigator

(a) Double-blind period

A total of 427 subjects were randomized to placebo (144), opicapone 25 mg (129), opicapone 50 mg (154). Except 1 subject in the opicapone 50 mg group, 426 subjects (144, 129, and 153) received the study drug. Of the 426, 15 subjects at Study Site [redacted][6)] were excluded, and the remaining 411 subjects (136, 125, and 150) were included in the safety analysis set. Except 4 subjects (1, 0, and 3) who were not assessed for the primary efficacy endpoint, 407 subjects (135, 125, and 147) were included in the FAS and subjected to the primary efficacy analysis. Treatment discontinuation occurred in 51 subjects (14, 11, and 26) for main reasons of "adverse events" in 31 subjects (9, 5, and 17) and "consent withdrawal" in 6 subjects (1, 3, and 2).

Table 43 shows the change from baseline in OFF-time[4)] at the end of the treatment phase (12 weeks after the completion of the levodopa dose adjustment period), the primary endpoint for the study. The results indicated

[6)] Due to the low validity of the data, the sponsor decided to discontinue the clinical trial at the study site.

a significant difference between the placebo and opicapone 50 mg (P = 0.0081) but not between the placebo and opicapone 25 mg (P = 0.1061).

Table 43. Change from baseline in OFF-time (minutes) at the end of the treatment phase (FAS LOCF)

	Placebo	Opicapone 25 mg	Opicapone 50 mg
Baseline Mean ± standard deviation	(n = 135) 367.4 ± 139.57	(n = 125) 372.4 ± 134.46	(n = 147) 379.2 ± 133.46
At the end of treatment phase Mean ± standard deviation	(n = 135) 302.9 ± 183.15	(n = 125) 269.7 ± 190.14	(n = 147) 255.3 ± 173.22
Change from baseline Least squares mean ± standard error[a]	−64.46 ± 14.35	−101.67 ± 14.86	−118.77 ± 13.81
Difference from placebo in change Least squares mean [95% CI][a]	—	−37.21 [−80.82, 6.40]	−54.31 [−96.18, −12.44]

a, ANCOVA using treatment group and region as factors, and baseline OFF-time as a covariate
Dunnett's test was used to adjust for multiplicity (two-sided significance level of 5%).

The incidence of adverse events was 64.0% (87 of 136 subjects) in the placebo group, 69.6% (87 of 125 subjects) in the opicapone 25 mg group, and 72.0% (108 of 150 subjects) in the 50 mg group. Major adverse events are listed in Table 44.

Table 44. Adverse events with an incidence of ≥5% in at any group (safety analysis set)

	Placebo (n = 136)	Opicapone 25 mg (n = 125)	Opicapone 50 mg (n = 150)
Dyskinesia	8.1 (11)	24.0 (30)	24.0 (36)
Dry mouth	0.7 (1)	10.4 (13)	4.0 (6)
Constipation	1.5 (2)	9.6 (12)	6.7 (10)
Insomnia	2.2 (3)	8.0 (10)	1.3 (2)
Parkinson's disease	5.1 (7)	7.2 (9)	4.0 (6)
Hypertension	2.2 (3)	6.4 (8)	4.0 (6)
Nausea	5.9 (8)	6.4 (8)	3.3 (5)
Fall	6.6 (9)	5.6 (7)	4.7 (7)
Headache	6.6 (9)	4.8 (6)	4.0 (6)
Blood CK increased	3.7 (5)	4.0 (5)	8.0 (12)
Urinary tract infection	1.5 (2)	2.4 (3)	6.0 (9)

% (number of subjects)

A death occurred in the placebo group (pneumonia), for which a causal relationship to the study drug was ruled out.

Serious adverse events (including death) occurred in 5 subjects in the placebo group (femoral neck fracture/pneumonia, radius fracture, ovarian cancer, cognitive disorder, and renal failure), 4 subjects in the opicapone 25 mg group (osteoarthritis, dyskinesia, renal failure acute, and urinary retention), and 9 subjects in the 50 mg group (nausea, cholecystitis acute, pyelonephritis acute, fall/head injury, biopsy prostate, basal cell carcinoma, delirium febrile/pleural effusion, cystocele, and pulmonary embolism). A causal relationship to the study drug could not be ruled out for radius fracture and cognitive disorder in the placebo group, dyskinesia in the opicapone 25 mg group, and nausea in the 50 mg group.

Adverse events led to treatment discontinuation of the study drug in 10 subjects in the placebo group (Parkinson's disease [2], dyskinesia, vomiting, cognitive disorder, rash maculo-papular, hepatic enzyme increased, pneumonia, ovarian cancer, and blood CK increased), 5 subjects in the opicapone 25 mg group (dyskinesia, dyskinesia/hallucination visual, tremor, nausea/headache/dizziness/palpitations, and blood CK increased), and 18 subjects in the 50 mg group (dyskinesia [5], dyskinesia/anxiety, dyskinesia/nausea, dyskinesia/tremor/blood CK increased, dizziness/fall, muscle spasms, pulmonary embolism, energy increased, abdominal pain upper/headache/vomiting, muscle spasms/nausea/abnormal dreams/paraesthesia/vomiting, abdominal pain/vomiting, cholecystitis acute/endoscopic retrograde cholangiopancreatography, loss of consciousness, and pleural effusion/delirium febrile).

(b) Open-label period

A total of 367 subjects entered the open-label period and received the study drug (365 completed the double-blind period, 2 terminated the double-blind period early due to shortage of the study drug). Of the 367 subjects, except 14 subjects at Study Site [redacted],[6)] 353 subjects were included in the safety analysis set. Of these, except 5 subjects who were not assessed for the primary efficacy endpoint and 9 subjects at Study Site [redacted],[6)] 339 subjects were included in the FAS for the primary efficacy analysis. Treatment discontinuation occurred in 81 subjects. The major reasons for discontinuation were "adverse events" in 32 subjects, "participants at Study Site [redacted]" in 13 subjects, "study withdrawal" in 10 subjects, "participants at Study Site [redacted]" in 9 subjects, and "lack of efficacy" in 5 subjects.

Table 45 shows the change from baseline in OFF-time in the double-blind phase.

Table 45. Change from baseline in OFF-time (minutes) (FAS, LOCF)

	Opicapone group		
	N	Absolute time	Change[a]
Baseline in the double-blind period	339	373.1 ± 133.48	—
Week 52 in the open-label period	339	246.8 ± 180.66	−126.3 ± 177.31

Mean ± standard deviation
a, change from baseline of the double-blind period

The incidence of adverse events was 75.9% (268 of 353 subjects), and major adverse events are listed in Table 46.

Table 46. Adverse events with an incidence of ≥5% (safety analysis set)

	Opicapone group (n = 353)
Dyskinesia	21.5 (76)
Parkinson's disease	17.0 (60)
Fall	9.1 (32)
Blood CK increased	7.4 (26)
Insomnia	5.7 (20)
Orthostatic hypotension	5.4 (19)

% (number of subjects)

Death occurred in 5 subjects (skull fractured base/cerebral haemorrhage/craniocerebral injury, cerebral haemorrhage, septic shock, small cell lung cancer, and death), and a causal relationship to the study drug could not be ruled out for skull fractured base/cerebral haemorrhage/craniocerebral injury.

Serious adverse events (including deaths) occurred in 39 subjects, and those that occurred in >1 subjects were pyrexia, fall, head injury, back pain, cerebral haemorrhage, and confusional state in 2 subjects each. A causal relationship to the study drug could not be ruled out for skull fractured base/cerebral haemorrhage/craniocerebral injury, diarrhoea/orthostatic hypotension, dyskinesia/confusional state, head injury, atrioventricular block complete, depression, abnormal behaviour, hallucination auditory, and agitated depression in 1 subject each.

Adverse events led to treatment discontinuation of the study drug in 29 subjects, and those that occurred in >1 subjects were Parkinson's disease in 4 subjects; and cerebral haemorrhage, dyskinesia, and hallucination in 2 subjects each.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about the clinical positioning of opicapone in the treatment of PD:

Parkinson's disease is a progressive neurodegenerative disorder. Major motor symptoms include bradykinesia, resting tremor, and rigidity. Currently, Parkinson's disease is treated with dopamine replacement therapies mainly with levodopa. In these therapies for the early stage of PD, patients first experience a honeymoon period of the first several years with favorable response to the pharmacotherapy, but as the effect of dopamine replacement therapies gradually decreases and patients suffer wearing-off phenomenon and motor complications such as dyskinesia. According to the "*Parkinson's disease treatment guideline* 2018 [in Japanese]," when response time to levodopa becomes shorter and wearing-off phenomenon develops with symptom progression, the first measure to take is to increase the dose of levodopa (4-5 times/day) or to start or increase the dose of a dopamine agonist, followed by the use of an additional dopamine-related drug such as COMT inhibitors. A COMT inhibitor is a dopamine-related drug that inhibits the activity of COMT, which is an alternative pathway for levodopa metabolism. A COMT inhibitor increases the bioavailability of levodopa, thereby reducing OFF-time caused by the wearing-off phenomenon. Entacapone, a COMT inhibitor currently used in the clinical practice in Japan, requires several doses daily together with levodopa/DCI because of its shorter half-life. In contrast, opicapone has long-lasting COMT inhibition activity and thus a single daily dose will suffice to reduce OFF-time.

In Foreign Study 301, the efficacy and safety of opicapone were compared with those of entacapone, and the non-inferiority of opicapone to entacapone was demonstrated in terms of the change from baseline in OFF-time, the primary endpoint of the study [see Section "7.3.1 Foreign phase III study (1)"]. The safety data indicated no significant differences between the entacapone 200 mg and opicapone 50 mg groups in the

frequency of adverse events (56.6% in the entacapone group and 53.9% in the opicapone 50 mg group) or serious adverse events (6.6% in the entacapone group and 3.5% in the opicapone 50 mg group). While the incidence of dyskinesia was higher in the opicapone 50 mg group (15.7%) than in the entacapone 200 mg group (8.2%), the difference was observed in mild events. In addition, insomnia, nausea, and constipation were identified as adverse events with an incidence of ≥5% in either group; however, the incidence of the adverse events did not differ greatly between the groups. Because both groups did not show clearly different trends in the frequency and severity of adverse events, the difference in the safety profiles between opicapone and entacapone was considered insignificant. In terms of the dosage regimens, opicapone is meant for bedtime dosing, which increases the daily total number of doses including levodopa as compared with entacapone. Entacapone, however, is not necessarily administered simultaneously with each dose of levodopa/DCI, and its dose level and the number of doses are adjusted according to the patient's symptoms and response to the drug (*Clinical neurology*. 2013;53:1348-50, *The Journal of the Japanese Society of Internal Medicine.* 2014;103:637-44). In the therapy with opicapone, the dose level and the number of doses need to be adjusted only with levodopa/DCI, therefore, opicapone is still considered useful even with its total number of doses increase. Thus, the difference in the efficacy and safety between opicapone and entacapone is negligible, and the choice between the 2 drugs will be made based primarily on their dosage regimens. As with the conventional COMT inhibitors, opicapone is expected to provide a treatment option for wearing-off phenomenon in patients with advanced PD.

PMDA's view:

Based on the results from clinical studies in Japan and other countries, and opicapone's mechanism of action, the combination use of opicapone with levodopa is expected to improve wearing-off phenomenon in patients with advanced-stage PD as does entacapone, a marketed COMT inhibitor. Regarding the selection of either opicapone or entacapone, based on the differences and similarities in the efficacy and safety profiles between the 2 drugs in Foreign Study 301 as well as the dosage regimen of opicapone being once daily at bedtime, it is expected that opicapone or entacapone will be selected according to the patient's condition, concomitant drugs, etc. Therefore, opicapone can be a treatment option for patients with advance-stage PD experiencing wearing-off. The expected efficacy and eligibility for opicapone will be further discussed in Sections "7.R.3 Efficacy," and "7.R.5 Indication."

7.R.2 Appropriateness of the developmental strategy with a bridging approach and the validity of bridging

The applicant's explanation:

For extrinsic ethnic factors, the UKPDS Brain Bank Clinical Diagnostic Criteria released in 1992 have been widely used as diagnosis criteria of PD globally including in Japan. Currently, new criteria developed by the International Parkinson and Movement Disorder Society (MDS) in 2015 are used in Japan and other countries. Pathologically, no significant difference are seen between Japanese and non-Japanese patients in time to onset and incidence of wearing-off phenomenon in PD after the initiation of levodopa therapy. The therapeutic approaches for the disease in Japan also do not differ largely from those in other countries. While drugs such

as istradefylline and zonisamide are available only in Japan, the primary use of levodopa and dopamine agonists for wearing-off phenomenon and the recommendation of addition of a COMT inhibitor are consistent between Japan and other countries. In terms of intrinsic ethnic factors, at the planning stage of Japanese Study 02, the PK of opicapone in the Japanese population was thought to be similar to those of the non-Japanese population based on the results of Study BIA-91067-126 conducted in Japanese and non-Japanese healthy adults. The extrapolation of the results from Foreign Study 301 to the Japanese patients was considered workable if Foreign Study 302 was used for bridging, and when Japanese Study 02 was able to meet the following bridging criteria.

- The primary endpoint analysis indicated the superiority of opicapone over placebo, and the dose-response relationship does not differ significantly from that of Foreign Study 302.
- Details of adverse events occurring in Japanese Study 02 do not differ significantly from those in Foreign Study 302.

In Japanese Study 02, the change from baseline in OFF-time, the primary efficacy endpoint, improved significantly in the opicapone 25 mg and 50 mg groups as compared with placebo; however, the 50 mg group did not show efficacy greater than in the 25 mg group. In contrast, Foreign Study 302 used for bridging showed that only the opicapone 50 mg group had significant improvement in OFF-time relative to placebo. Safety analyses showed that dyskinesia was the only adverse event with an incidence higher than placebo in both Japanese Study 02 and Foreign Study 302, and no noteworthy differences were observed in terms of the occurrence of adverse events.

The following aspects were investigated to identify the factors leading to the differences in efficacy results between the studies conducted in Japan and overseas as described above.

(a) Differences in the PK between Japanese and non-Japanese populations and exposure-response relationship of opicapone

The PK data of opicapone in Japanese and non-Japanese populations were re-evaluated. The results suggested that the absorption of opicapone may vary by environmental factors including dietary habits differing from one region to another; exposure to opicapone in Japanese subjects who were treated with opicapone tablets was twice the level in Caucasian subjects treated with opicapone capsules (a marketed formulation) of the equivalent strength [see Section “6.R.1 Differences in PK of opicapone between Japanese and non-Japanese populations”]. However, results of analyses, including a PPK/pharmacodynamic (levodopa exposure) analysis to evaluate the exposure-response relationship in Japanese and non-Japanese populations as well as another analysis to evaluate the relation between levodopa exposure and change in OFF-time suggested that, in the Japanese population, opicapone is expected to have efficacy at a level comparable to that in non-Japanese populations with equivalent opicapone exposure.

(b) Effect of different patient characteristics between studies

Demographic characteristics of subjects in the clinical studies in Japan and overseas were compared. In response to the results that revealed differences in the daily dose of levodopa and kinds of coadministered

drugs, the effects of these factors on the efficacy of opicapone were evaluated. Table 47 shows the results of subgroup analysis by levodopa daily dose category. Although the distribution of subjects across the categories vary between the Japanese and overseas studies, in the subgroup receiving levodopa ≥700 mg daily in Japanese Study 02, subjects treated with opicapone showed reduced OFF-time as compared with those receiving placebo, with the exception of those receiving opicapone 25 mg, who were small in number. Therefore, it was considered unlikely that the difference in daily dose of levodopa affected the results in the Japanese or overseas studies.

Table 47. Change from baseline in OFF-time (minutes) at the final evaluation (double-blind period) by levodopa daily dose category (FAS)

Levodopa daily dose		Japanese Study 02			Foreign Study 301[c]			Foreign Study 302		
		Placebo	Opicapone 25 mg	Opicapone 50 mg	Placebo	Opicapone 25 mg	Opicapone 50 mg	Placebo	Opicapone 25 mg	Opicapone 50 mg
<400 mg	N	65	64	59	16	16	17	17	13	21
	Change from baseline[a, b]	−37.61 ± 18.93	−80.03 ± 19.10	−62.00 ± 19.79	−42.75 ± 32.45	−41.85 ± 32.56	−115.11 ± 31.53	−27.75 ± 27.97	−77.57 ± 32.25	−66.66 ± 25.12
≥400 mg and <500 mg	N	38	40	39	16	23	12	19	16	15
	Change from baseline[a, b]	−1.53 ± 23.93	−82.72 ± 23.27	−56.87 ± 23.59	−57.25 ± 34.86	−87.03 ± 29.08	−97.58 ± 40.25	−59.59 ± 34.69	−114.10 ± 37.82	−173.48 ± 39.05
≥500 mg and <700 mg	N	34	32	32	35	32	37	35	25	41
	Change from baseline[a, b]	−23.91 ± 28.80	−60.40 ± 29.69	−45.61 ± 29.69	−16.41 ± 23.82	−84.61 ± 24.93	−109.96 ± 23.28	−70.32 ± 27.99	−134.74 ± 33.34	−147.20 ± 25.80
≥700 mg	N	10	7	15	53	45	49	64	71	70
	Change from baseline[a, b]	−32.63 ± 46.67	34.02 ± 55.41	−107.46 ± 37.78	−80.65 ± 21.35	−97.37 ± 23.20	−122.03 ± 22.00	−76.22 ± 20.72	−94.34 ± 19.75	−112.80 ± 19.88

a, least squares mean ± standard error
b, ANCOVA using treatment group as a factor and baseline OFF-time as a covariate
c, an ANOCOVA was performed by specifying 5 treatment groups (placebo, opicapone 5 mg, 25 mg, 50 mg, and entacapone 200 mg group), and the table presents the results of the placebo, opicapone 25 mg, and 50 mg groups only.

Dopamine agonists were coadministered in approximately 80% of subjects in Japanese Study 02, and approximately 70% in Foreign Studies 301 and 302. MAO-B inhibitors were coadministered in approximately 50% of subjects in Japanese Study 02, and approximately 20% in Foreign Studies 301 and 302. Subgroup analyses by with or without coadministered drugs have indicated OFF-time reduction in the opicapone groups as compared to placebo in all studies regardless of a dopamine agonist or an MAO-B inhibitor. Therefore, it is considered unlikely that the efficacy results were affected by these drugs.

Based on the investigation results of (a) and (b), the results of the efficacy evaluation of opicapone were unlikely to be affected by differences in patient characteristics in Japanese and foreign studies. It is considered that the dose-response curve shown in Foreign Study 302 shifted toward the lower dose area in Japanese Study 02 because of the differences in the PK of opicapone.

PMDA's view:

Unlike Foreign Study 302, Japanese Study 02 revealed a tendency of leveling-off in efficacy at >25 mg of opicapone. Albeit from a retrospective viewpoints, opicapone exposure in Japanese subjects following a dose of opicapone tablet were approximately 2-fold that in Caucasian subjects receiving the equivalent dose of opicapone capsule (a marketed formulation overseas), and this difference may have contributed to the tendency. It would have been more appropriate to investigate differences in exposure between Japanese and non-Japanese populations using data not only from Study BIA-91067-126 but also from other clinical studies so as to determine more appropriate dose levels to investigate (including <25 mg) before planning Japanese Study 02 as the bridging study. Nevertheless, regardless of dissimilarity in the levodopa dose levels and drugs coadministered among the clinical studies conducted in Japan and overseas, the differences in ethnic factors except opicapone exposure had limited influence on the results of Japanese Study 02. Given that the demonstrated OFF-time reduction effect in the opicapone 25 mg group is similar to that in the 50 mg group, and based on the investigation results on the difference in opicapone exposure between Japanese and Caucasian subjects, the dose-response curve of Japanese subjects shifting toward the lower dose area from that of Caucasian subjects is presumed to indicate that the efficacy of opicapone 50 mg in the foreign clinical studies is equivalent to the that of opicapone 25 mg in Japanese Study 02. From a comprehensive viewpoint and based on observations below, the bridging was satisfactory and enabled the extrapolation of foreign data from Foreign Studies 301 and 302 to Japanese patients with PD for efficacy evaluation of opicapone. The adequacy of the above discussion will be finalized taking into account the comments from the Expert Discussion.

- In Japanese Study 02, change from baseline in OFF-time, the primary endpoint, demonstrated the superiority of opicapone 25 mg and 50 mg over placebo.
- Change from baseline in OFF-time in the opicapone 25 mg group in Japanese Study 02 is considered comparable to that in the opicapone 50 mg group in Foreign Study 302.
- No significant differences are observed in the occurrence of adverse events between Japanese Study 02 and Foreign Study 302 [see Section “7.R.4 Safety”].

7.R.3 Efficacy

The applicant’s explanation about the efficacy of opicapone for the treatment of wearing-off phenomenon in patients with PD treated with levodopa:

Japanese Study 02, the bridging study, in patients with PD experiencing wearing-off while treated with levodopa/DCI demonstrated a significant difference in change from baseline in OFF-time between opicapone 25 mg or 50 mg and placebo (Table 32). Foreign Study 302 used for bridging also demonstrated a significant difference between opicapone 50 mg and placebo in the same primary endpoint in the same study population (Table 43). Foreign Study 301 demonstrated the superiority of opicapone 50 mg over placebo as well as non-inferiority to entacapone [see Section “7.3.1 Foreign phase III study (1)”], indicating that the efficacy of opicapone is not inferior to entacapone. Table 48 shows the relationship between the change from baseline in OFF-time and change in overall symptoms in Japanese Study 02. As shown, OFF-time reduction tends to be related to subjective improvement in overall symptoms. In a Japanese phase III study of an existing anti-PD drug with the primary endpoint of change from baseline in OFF-time, the difference between the active drug

and placebo was −44.4 to −50.4 minutes. Therefore, the difference in change from baseline in OFF-time of opicapone 25 mg from that of placebo, −44.68 minutes, is considered clinically significant.

Table 48. Relationship between the change from baseline in OFF-time (minutes) at the final evaluation (double-blind period) in Japanese Study 02 and change in overall symptoms (FAS)

		% (number of subjects)	Change from baseline in OFF-time[a]
Change in overall symptoms[b]	Very much improved	2.1 (9)	−217.8 ± 203.7
	Much improved	12.6 (55)	−152.7 ± 129.6
	Minimally improved	33.1 (144)	−87.3 ± 166.0
	No change	35.4 (154)	−16.2 ± 128.6
	Minimally worse	12.0 (52)	31.8 ± 156.1
	Much worse	2.8 (12)	38.3 ± 204.5
	Very much worse	0.7 (3)	363.3 ± 295.4
	Not assessed	0.5 (2)	−240.0 ± 84.9
	Missing data	0.9 (4)	−2.5 ± 115.3

a, mean ± standard deviation
b, subject's self-assessment

PMDA concluded that opicapone has efficacy in the treatment of wearing-off phenomenon in Japanese patients with PD treated with levodopa, based on the bridging of Japanese Study 02 to Foreign Study 302 that is considered satisfactory [see Section "7.R.2 Appropriateness of the developmental strategy with a bridging approach and the validity of bridging"]; opicapone's superiority to placebo and non-inferiority to entacapone, at its recommended clinical doses, in change from baseline in OFF-time demonstrated in the Japanese and foreign clinical studies (25 mg for Japanese and 50 mg for non-Japanese; see Section "7.R.6 Dosage and administration"), and on the applicant's explanation that the OFF-time reduction effect achieved with opicapone is considered clinically significant.

7.R.4 Safety

7.R.4.1 Dyskinesia

The applicant's explanation about dyskinesia:

Table 49 shows the occurrence of dyskinesia in the clinical studies conducted in Japan and overseas (Japanese Study 02 and Foreign Studies 301 and 302). The incidence of dyskinesia tended to be higher in the opicapone group than in the placebo group. In Foreign Study 301, the incidence of dyskinesia tended to be higher in the opicapone 50 mg group than in the entacapone 200 mg group (Table 40). The majority of the events of dyskinesia reported in the clinical studies in Japan and overseas were mild or moderate in severity, and the trends in the occurrence of dyskinesia between Japan and overseas were similar.

A total of 8 cases (including 3 serious cases) of dyskinesia have been reported in the overseas the post-marketing[7)] setting as related adverse reactions.

[7)] Survey period: [redacted], 20[redacted] to [redacted], 20[redacted], estimated number of patients exposed, 15164 person-year

Opicapone-associated dyskinesia is considered clinically acceptable in light of the frequency and severity identified in the Japanese and foreign clinical studies. However, because dyskinesia is thought to be induced by dopamine receptor stimulation and opicapone increases the bioavailability of levodopa, the risk of dyskinesia is expected to increase with the use of opicapone. Therefore, cautionary advice should be given in the "Precautions Concerning Dosage and Administration" section in the package insert, etc. on the risk of developing dyskinesia and measures to be taken at its onset, as done for entacapone.

Table 49. Incidences of dyskinesia in the clinical studies conducted in Japan and overseas (safety analysis set)

	Japanese Study 02				Foreign phase III[a]			
	Double-blind period			Open-label period	Double-blind period			Open-label period
	Placebo (n = 147)	Opicapone 25 mg (n = 145)	Opicapone 50 mg (n = 145)	Opicapone 50 mg (n = 391)	Placebo (n = 257)	Opicapone 25 mg (n = 244)	Opicapone 50 mg (n = 265)	Opicapone (n = 848)
Dyskinesia	2.7 (4)	9.0 (13)	12.4 (18)	12.0 (47)	6.2 (16)	16.0 (39)	20.4 (54)	17.5 (148)
Serious adverse events	0 (0)	0 (0)	0.7 (1)	0.3 (1)	0 (0)	0.4 (1)	0.4 (1)	0.1 (1)
Adverse events leading to treatment discontinuation	0.7 (1)	0.7 (1)	1.4 (2)	0 (0)	0.4 (1)	0.8 (2)	3.0 (8)	0.7 (6)

% (number of subjects)
a, pooled data from Foreign Studies 301 and 302

PMDA's view:

Given the action mechanism of opicapone, dopaminergic adverse events are expected. Data from the Japanese and foreign clinical studies indicated that the incidence of dyskinesia tends to increase with increasing dose of opicapone, and therefore, patients should be monitored for the development of dyskinesia during opicapone treatment. In Foreign Study 301, as compared with the entacapone 200 mg group, the incidence of dyskinesia was higher in the opicapone 50 mg group, the recommended dose overseas. However, given that no clinical study data directly comparing opicapone 25 mg, the likely recommended clinical dose in Japan [see Section "7.R.6 Dosage and administration"] with entacapone 100 mg, the usual dose in Japan, and that the majority of the events of dyskinesia reported in the clinical studies in Japan and overseas were mild or moderate in severity and tolerable, it cannot be clearly ascertained that opicapone has a higher risk of dyskinesia than entacapone. Thus, the applicant's proposal to provide cautionary advice via the package insert as with entacapone is appropriate.

7.R.4.2 Impulse-control disorders

The applicant's explanation about impulse-control disorders:

In Japanese Study 02, no impulse-control disorders occurred in the double-blind period, and only 1 subject in the open-label period reported impulse-control disorder. In foreign phase III studies,[8)] impulse-control disorders occurred in 2 subjects in the opicapone 50 mg group (pathological gambling [1] and impulsive behaviour [1]) in the double-blind period and 9 subjects in the open-label period (pathological gambling [4], compulsive shopping [2], impulsive behaviour [2], and impulse-control disorder [1]). Although no serious

[8)] Pooled data from Foreign Study 301 (double-blind period) and Foreign Study 302 (double-blind period)

impulse-control disorders occurred, an event led to treatment discontinuation in 1 subject (pathological gambling) in the open-label period of the foreign phase III studies.

Impulse-control disorder has been reported as a related adverse reaction (1 non-serious case) in the overseas post-marketing[7)] setting.

Impulse-control disorders may be triggered by overstimulation of the central dopamine system, dopamine D_3 receptor stimulation in particular, due to the dose of levodopa or other drugs increased with disease progression (*Neurological Therapeutics.* 2017;34:151-4). The package inserts of levodopa formulations and dopamine agonists give caution against the potential risk of pathological gambling, increased pathological sexual desire, compulsive shopping, overeating, and other impulse-control disorders. The use of opicapone enhances the bioavailability of levodopa and may trigger similar symptoms. Therefore, appropriate actions, including the discontinuation of opicapone, in case of impulse-control disorder, should be advised via the package insert.

PMDA's view:
Although the incidences of impulse-control disorder-related adverse events were low in the clinical studies conducted in Japan and overseas, a relationship between the events to opicapone treatment is presumed. Furthermore, once developed, impulse-control disorders may seriously affect not only the patient but also everyday lives and finance of their family members. Therefore, it is appropriate to provide cautionary advice via the package insert as proposed by the applicant.

7.R.4.3 Other dopaminergic adverse events
The applicant's explanation:
Other than the risks focused in Sections "7.R.4.1 Dyskinesia" and "7.R.4.2 Impulse-control disorders," "psychiatric symptoms such as hallucination and delusion," "orthostatic hypotension," "somnolence and sudden onset of sleep," and "nausea and vomiting" are also dopaminergic adverse events. The observations of (a) through (d) below indicate that these events may be clinically acceptable. Nevertheless, opicapone can increase the bioavailability of levodopa and can trigger these events. Therefore, cautionary advice will be provided on these events in the package insert.

(a) Psychiatric symptoms such as hallucination
Table 50 shows the incidences of psychiatric symptom-related adverse events[9)] reported in the clinical studies in Japan and overseas (Studies 02, 301, and 302). While the incidences tended to be higher in the opicapone group as compared with placebo, the trend in the occurrence of events were similar between Japan and overseas.

Related adverse reactions have been reported in the overseas post-marketing[7)] survey, including hallucination (11; including 2 serious cases), hallucination visual (8; including 1 serious case), psychotic disorder (5;

[9)] MedDRA SMQ "psychosis and psychotic disorders"

including 1 serious case), paranoia (3; including 1 serious case), substance-induced psychotic disorder (1 serious case), and abnormal behaviour (1 serious case).

Table 50. Incidences of psychiatric symptom-related adverse events in the clinical studies conducted in Japan and overseas (safety analysis set)

	Japanese Study 02				Foreign phase III[a] Studies			
	Double-blind period			Open-label period	Double-blind period			Open-label period
	Placebo (n = 147)	Opicapone 25 mg (n = 145)	Opicapone 50 mg (n = 145)	Opicapone 50 mg (n = 391)	Placebo (n = 257)	Opicapone 25 mg (n = 244)	Opicapone 50 mg (n = 265)	Opicapone (n = 848)
Psychiatric symptom-related adverse events	0.7 (1)	4.1 (6)	3.4 (5)	6.6 (26)	1.2 (3)	5.3 (13)	4.2 (11)	4.6 (39)
Hallucination	0.7 (1)	2.1 (3)	1.4 (2)	4.3 (17)	0.4 (1)	2.5 (6)	1.1 (3)	1.7 (14)
Hallucination visual	0 (0)	2.8 (4)	2.1 (3)	2.0 (8)	0.8 (2)	1.6 (4)	2.3 (6)	1.5 (13)
Hallucination auditory	0 (0)	0 (0)	0 (0)	0.8 (3)	0 (0)	0.8 (2)	0.4 (1)	0.4 (3)
Serious adverse events	0 (0)	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)	0 (0)	0.4 (3)
Adverse events leading to treatment discontinuation	0 (0)	1.4 (2)	2.1 (3)	0.5 (2)	0 (0)	1.2 (3)	0.8 (2)	0.7 (6)

% (number of subjects)
a, pooled data from Foreign Studies 301 and 302

(b) Orthostatic hypotension

Table 51 shows the incidences of orthostatic hypotension in the clinical studies in Japan and overseas (Studies 02, 301, and 302). While the incidence tended to be higher in the opicapone groups as compared with placebo, all reported events were either mild or moderate in severity, and the trends in the occurrence of the events were similar between Japan and overseas.

No related adverse reactions have been reported in the overseas post-marketing[7)] survey.

Table 51. Incidences of orthostatic hypotension in the clinical studies conducted in Japan and overseas (safety analysis set)

	Japanese Study 02				Foreign phase III[a] Studies			
	Double-blind period			Open-label period	Double-blind period			Open-label period
	Placebo (n = 147)	Opicapone 25 mg (n = 145)	Opicapone 50 mg (n = 145)	Opicapone 50 mg (n = 391)	Placebo (n = 257)	Opicapone 25 mg (n = 244)	Opicapone 50 mg (n = 265)	Opicapone (n = 848)
Orthostatic hypotension	0 (0)	2.8 (4)	2.8 (4)	2.8 (11)	0 (0)	0.8 (2)	1.5 (4)	4.1 (35)
Serious adverse events	0 (0)	0 (0)	0.7 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0.1 (1)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.2 (2)

% (number of subjects)
a, pooled data from Foreign Studies 301 and 302

(c) Somnolence and sudden onset of sleep

Table 52 shows the incidence of somnolence and sudden onset of sleep in the clinical studies conducted in Japan and overseas (Studies 02, 301, and 302). While the incidences tended to be higher in the opicapone groups as compared with placebo, all reported events were either mild or moderate in severity, and the trends in the occurrence of the events were similar between Japan and overseas.

Somnolence has been reported as related adverse reactions (7 including 2 serious cases) in the overseas post-marketing[7)] survey.

Table 52. Incidences of somnolence and sudden onset of sleep in the clinical studies in Japan and overseas (safety analysis set)

	Japanese Study 02				Foreign phase III[a] Studies			
	Double-blind period			Open-label period	Double-blind period			Open-label period
	Placebo (n = 147)	Opicapone 25 mg (n = 145)	Opicapone 50 mg (n = 145)	Opicapone 50 mg (n = 391)	Placebo (n = 257)	Opicapone 25 mg (n = 244)	Opicapone 50 mg (n = 265)	Opicapone (n = 848)
Somnolence	0.7 (1)	2.8 (4)	2.1 (3)	1.3 (5)	1.9 (5)	4.1 (10)	1.9 (5)	0.9 (8)
Sudden onset of sleep	0 (0)	0 (0)	0 (0)	1.3 (5)	0 (0)	0 (0)	0 (0)	0.1 (1)
Serious adverse events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

% (number of subjects)
a, pooled data from Foreign Studies 301 and 302

(d) Nausea and vomiting

Table 53 shows the incidences of nausea and vomiting reported in the clinical studies in Japan and overseas (Studies 02, 301, and 302). While the incidences tended to be higher in the opicapone group as compared with placebo, the trends in the occurrence of the events were similar between Japan and overseas.

Related adverse reactions have been reported in the overseas post-marketing[7)] survey: nausea (10 including 1 serious case) and vomiting (1 non-serious case).

Table 53. Incidences of nausea and vomiting in the clinical studies in Japan and overseas (safety analysis set)

	Japanese Study 02				Foreign phase III[a] Studies			
	Double-blind period			Open-label period	Double-blind period			Open-label period
	Placebo (n = 147)	Opicapone 25 mg (n = 145)	Opicapone 50 mg (n = 145)	Opicapone 50 mg (n = 391)	Placebo (n = 257)	Opicapone 25 mg (n = 244)	Opicapone 50 mg (n = 265)	Opicapone (n = 848)
Nausea	1.4 (2)	4.1 (6)	4.8 (7)	1.5 (6)	3.9 (10)	4.5 (11)	3.0 (8)	2.6 (22)
Vomiting	0 (0)	0 (0)	2.1 (3)	2.0 (8)	1.9 (5)	1.2 (3)	1.9 (5)	0.8 (7)
Serious adverse events	0 (0)	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)	0.4 (1)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0.3 (1)	0.4 (1)	0.8 (2)	1.5 (4)	0.4 (3)

% (number of subjects)
a, pooled data from Foreign Studies 301 and 302

PMDA's view:

The incidences of dopaminergic adverse events shown in (a) through (d) above (psychiatric symptoms such as hallucination and delusion, orthostatic hypotension, somnolence and sudden onset of sleep, and nausea and vomiting) tended to be higher with opicapone as compared with placebo. In light of the action mechanism of opicapone, these are the adverse reactions of opicapone warranting caution in its use. Therefore, it is appropriate to provide cautionary advice in the package insert as proposed by the applicant.

7.R.4.4 Neuroleptic malignant syndrome and rhabdomyolysis

The applicant's explanation:

In Japanese Study 02, no neuroleptic malignant syndrome and rhabdomyolysis were reported in the double-blind period. In the open-label period, neuroleptic malignant syndrome and rhabdomyolysis were reported from 1 subject each, but neither event was serious. In the foreign phase III studies, neither neuroleptic malignant syndrome nor rhabdomyolysis was reported. Table 54 shows the incidences of blood CK increased. There were no trends toward increasing incidences in the opicapone groups as compared with placebo and no reports of serious adverse events.

No neuroleptic malignant syndrome-related adverse reactions have been reported in the overseas post-marketing[7)] survey, and 1 case (non-serious) of blood CK increased has been reported.

Although rare, there are few reports of neuroleptic malignant syndrome and rhabdomyolysis in patients with PD following abrupt withdrawal of levodopa. Withdrawal of opicapone, a dopamine-related drug, may lead to a consequence similar to the withdrawal of levodopa. Therefore, the potential risks of neuroleptic malignant syndrome and rhabdomyolysis as well as need for careful vigilance following the discontinuation of opicapone should be advised appropriately via the package insert.

Table 54. Incidences of blood CK increased in the clinical studies in Japan and overseas (safety analysis set)

	Japanese Study 02				Foreign phase III[a] Studies			
	Double-blind period			Open-label period	Double-blind period			Open-label period
	Placebo (n = 147)	Opicapone 25 mg (n = 145)	Opicapone 50 mg (n = 145)	Opicapone 50 mg (n = 391)	Placebo (n = 257)	Opicapone 25 mg (n = 244)	Opicapone 50 mg (n = 265)	Opicapone (n = 848)
Blood CK increased	2.0 (3)	0.7 (1)	2.1 (3)	2.3 (9)	1.9 (5)	2.9 (7)	4.9 (13)	4.5 (38)
Serious adverse events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0.4 (1)	0.4 (1)	0.4 (1)	0 (0)

% (number of subjects)
a, pooled data from Foreign Studies 301 and 302

PMDA concluded that the applicant's measures are appropriate.

7.R.4.5 Hepatic dysfunction

The applicant's explanation:

Table 55 shows the incidences of main adverse events related to drug-induced hepatic disorders[10)] observed following the administration of opicapone. There was no trend toward increasing incidence of drug-induced hepatic disorder-related adverse events or serious adverse events in the opicapone group as compared with placebo. In the clinical studies in Japan and overseas, patients were excluded from the studies if presenting with hepatic enzyme anomalies, AST or ALT >2-fold the upper limit of normal, at screening before

10) MedDRA SMQ "Drug related hepatic disorders - comprehensive search"

randomization or at laboratory testing during the screening period, and this hinders the investigation of safety in patients with hepatic impairment.

An adverse reaction related to drug-induced hepatic disorders (hepatitis cholestatic, 1 serious case) has been reported in the overseas post-marketing[7)] survey.

Based on data including results from the above clinical studies of opicapone, no clear hepatic dysfunction risk was identified. However, given that caution was advised for hepatic dysfunction as a clinically significant adverse reaction of entacapone, a similar drug, information about the occurrence of hepatic dysfunction should be collected in the post-marketing setting, and any new findings should be communicated to healthcare professionals in an appropriate manner.

Table 55. Incidences of main adverse events of hepatic dysfunction in the clinical studies in Japan and overseas (safety analysis set)

	Japanese Study 02				Foreign phase III[a] Studies			
	Double-blind period			Open-label period	Double-blind period			Open-label period
	Placebo (n = 147)	Opicapone 25 mg (n = 145)	Opicapone 50 mg (n = 145)	Opicapone 50 mg (n = 391)	Placebo (n = 257)	Opicapone 25 mg (n = 244)	Opicapone 50 mg (n = 265)	Opicapone (n = 848)
Adverse events related to drug-induced hepatic disorders	0.7 (1)	0 (0)	2.8 (4)	2.8 (11)	3.1 (8)	1.2 (3)	1.1 (3)	3.2 (27)
Haemangioma of liver	0.7 (1)	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic function abnormal	0.7 (1)	0 (0)	0.7 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic enzyme increased	0 (0)	0 (0)	0.7 (1)	0 (0)	0.8 (2)	0 (0)	0 (0)	0.1 (1)
γ-GTP increased	0 (0)	0 (0)	0 (0)	0.5 (2)	0.8 (2)	0.4 (1)	0 (0)	1.2 (10)
AST increased	0 (0)	0 (0)	0 (0)	0.5 (2)	0 (0)	0.4 (1)	0.8 (2)	0.8 (7)
ALT increased	0 (0)	0 (0)	0 (0)	0.5 (2)	0 (0)	0.8 (2)	0.8 (2)	0.4 (3)
Blood ALP increased	0 (0)	0 (0)	0.7 (1)	1.0 (4)	0.4 (1)	0 (0)	0 (0)	0.2 (2)
International normalised ratio increased	0 (0)	0 (0)	0 (0)	0.3 (1)	0.4 (1)	0 (0)	0 (0)	0.4 (3)
Prothrombin time prolonged	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4)
Serious adverse events	0 (0)	0 (0)	0 (0)	0.3 (1)	0.8 (2)	0 (0)	0 (0)	0.1 (1)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0.3 (1)	1.2 (3)	0 (0)	0 (0)	0 (0)

% (number of subjects)
a, pooled data from Foreign Studies 301 and 302

PMDA's view:

Results from the Japanese and foreign clinical studies of opicapone and overseas post-marketing reports have indicated no clear hepatic dysfunction risk associated with opicapone treatment. Therefore, information about the occurrence of hepatic dysfunction should be provided in the "Other Adverse Reactions" section of the package insert, while no additional cautionary advice is necessary at this time point. The applicant's proposal about the post-marketing information collection on the occurrence of hepatic dysfunction is appropriate in light of the adverse reaction information of the similar drug.

7.R.5 Indication

PMDA's view:

The results of discussions in Sections "7.R.3 Efficacy" and "7.R.4 Safety" indicated clinically significant efficacy and acceptable safety in patients with PD on levodopa/DCI experiencing wearing-off in the Japanese and foreign clinical studies. Therefore, the proposed indication of opicapone "improvement of end-of-dose motor fluctuations (wearing-off phenomenon) in patients with Parkinson's disease by combination use with levodopa-containing formulations" is largely appropriate. However, in Japan, products containing entacapone (a COMT inhibitor), levodopa, or carbidopa have also been approved as "levodopa-containing formulations." Opicapone should not be used in combination with other COMT inhibitors, and for this reason, the definition of the indication should be revised as below in order to avoid this improper combination use. The definition will be finalized taking into account the comments from the Expert Discussion.

Indication (proposed revision by PMDA; the underlined words are modified from the proposed text)

Improvement of end-of-dose motor fluctuations (wearing-off phenomenon) in patients with Parkinson's disease by combination use <u>with levodopa/carbidopa or levodopa/benserazide hydrochloride</u>

7.R.6 Dosage and administration

The applicant's explanation about the dosage regimen of opicapone:

(a) Dosing method

A dosing interval of ≥1 hour between opicapone and a levodopa-containing formulation is considered appropriate from the standpoint of pharmacodynamic action based on the following findings from the foreign phase I studies (Studies BIA-91067-117 and BIA-91067-118): (i) plasma levodopa $AUC_{0-\infty}$ was higher in the group receiving levodopa/carbidopa 1 hour after the administration of opicapone as compared to the group receiving opicapone and levodopa/carbidopa simultaneously (geometric mean ratio [90% CI], 1.09 [1.01, 1.16]); (ii) the ratio of levodopa $AUC_{0\text{-last}}$ when levodopa/carbidopa or levodopa/benserazide was administered 1 hour after opicapone relative to 1 hour after placebo was 1.39 to 1.78, indicating increased levodopa exposure.

To ensure a dosing interval of ≥1 hour between opicapone and the levodopa-containing formulation in patients with PD experiencing the wearing-off phenomenon who require several doses of the levodopa-containing formulation daily, bedtime dosing was considered the best.

Based on the above results, in the dosage regimens in Studies 02, 301, and 302, opicapone was administered once daily at bedtime ≥1 hour after the last daily dose of levodopa-containing formulation, for which efficacy and safety were demonstrated. Some patients are expected to take a levodopa-containing formulation at bedtime for the purpose of controlling the wearing-off phenomenon during the night and in the early morning (*Parkinson's disease treatment guideline* 2018). Increased levodopa exposure was observed when a levodopa-containing formulation was administered 1 hour after the opicapone dose in the foreign phase I study (Study BIA-91067-118). Given these, the administration order of opicapone and levodopa-containing formulation

need not be specified. Accordingly, it was considered appropriate to specify that opicapone should be administered ≥1 hour before or after administration of the last dose of the day of a levodopa-containing formulation.

(b) Dosage

In Foreign Studies 301 and 302, the efficacy of opicapone was evaluated using 50 mg [see Section "7.R.3 Efficacy"], and based on the results from the clinical studies conducted in Japan and overseas, the efficacy in the opicapone 50 mg group in the foreign clinical studies was thought to be equivalent to that in the opicapone 25 mg group in Japanese Study 02 [see Section "7.R.2 Appropriateness of the developmental strategy with a bridging approach and the validity of bridging"]. Safety analyses indicated that, in Japanese Study 02, the incidence of adverse events such as dyskinesia tended to be higher in the 50 mg group than in the 25 mg group. Based on the efficacy and safety evaluation results, it was considered that a recommended dose of 25 mg would be appropriate for Japanese patients.

(c) Long-term efficacy and safety of opicapone 25 mg

In the open-label period of Japanese Study 02, in which opicapone 50 mg was administered to Japanese patients with PD for an extended period, OFF-time reduction effect observed in the double-blind period lasted during the open-label period (Table 34). Given that, in the double-blind period of Japanese Study 02, change from baseline in OFF-time in the opicapone 50 mg group was similar to that in the opicapone 25 mg at all time points, long-term administration of opicapone 25 mg in Japanese patients with PD is also expected to be long lasting.

Safety analyses indicated that trends in the incidence of adverse events in the open-label period of Japanese Study 02 were similar to those in the double-blind period. In the double-blind period of Japanese Study 02, the incidence of dyskinesia tended to increase in an opicapone dose-dependent manner. However, tolerability in the opicapone 25 mg group did not differ greatly from that in the 50 mg group, long-term administration of opicapone 25 mg is thus less likely to increase particular risks.

PMDA's view on the discussions in (a), (b), and (c) above:

The applicant explained that opicapone and a levodopa-containing formulation should be administered ≥1 hour apart, which is appropriate based on the submitted data. Given that some patients with PD experiencing the wearing-off phenomenon take a levodopa-containing formulation 4 to 5 times daily or even more frequently according to the Parkinson's disease treatment guideline (2018), it is appropriate to specify bedtime dosing to ensure a sufficient dosing interval between opicapone and the levodopa-containing formulation. Furthermore, some patients may take a levodopa-containing formulation after opicapone, and based on the results of the foreign phase I study (Study BIA-91067-118), levodopa exposure is expected to increase when a levodopa-containing formulation is administered after opicapone. It is appropriate to set a dosing regimen so as to allow not only the administration of opicapone following a levodopa-containing formulation, but also the administration of opicapone ≥1 hour before the levodopa-containing formulation.

The recommended dose of 25 mg is appropriate for Japanese patients with PD in light of the differences in the PK between Japanese and non-Japanese populations, as well as the efficacy and safety results from Studies 02, 301 and 302. While opicapone 50 mg did not show higher efficacy than that of 25 mg in Japanese Study 02, and the risk for developing dyskinesia was higher at 50 mg than 25 mg. Therefore, it remains unclear whether the dose increase option should be included in the dosage regimen definition.

The adequacy of the above discussion will be finalized taking into account the comments from the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant's explanation:

To investigate the occurrence, etc. of dyskinesia associated with the clinical use of opicapone, the applicant planned a specified use-results survey with a follow-up period of 52 weeks and a target sample size of 250 patients (safety analysis set). Based on the incidence of dyskinesia in the opicapone 25 mg group in Japanese Study 02 (double-blind period), 9.0% (13 of 145 subjects), the sample size of 250 is considered suffice to investigate the frequency of dyskinesia occurring as adverse reactions.

PMDA's view:

While the post-marketing surveillance planned by the applicant is generally adequate, hallucination, hallucination visual, and orthostatic hypotension should also be subjected to data collection in addition to dyskinesia. The details of post-marketing surveillance, as well as the identification of safety specification, adequacy of risk classification, and the appropriateness of pharmacovigilance activities and risk minimization activities will be finalized in accordance with the "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-1, and PFSB/ELD Notification No. 0411-2, dated April 11, 2012) taking into account the comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that opicapone has efficacy in the treatment of end-of-dose motor fluctuations (wearing-off phenomenon) in patients with PD, and that opicapone has acceptable safety in view of its benefits. Opicapone is a COMT inhibitor, which allows once daily treatment, and is of clinical significance as it offers a new treatment option for patients with PD experiencing end-of-dose motor fluctuations (wearing-off phenomenon). PMDA considers that the validity of bridging data, indication, dosage and administration, and post-marketing investigations are subject to further discussions.

PMDA has concluded that opicapone may be approved if opicapone is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 12, 2020

Product Submitted for Approval

Brand Name	Ongentys Tablets 25 mg
Non-proprietary Name	Opicapone
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	February 27, 2019

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Appropriateness of the developmental strategy with a bridging approach and the validity of bridging

The comment made by the expert advisor on the validity of bridging data:

While the predefined requirements for bridging have not been satisfactorily met, the bridging is considered valid based on re-examined difference in the PK of opicapone between Japanese and non-Japanese populations and the comparison of efficacy between Japanese and non-Japanese populations at the recommended dose in respective studies. The expert advisors supported the PMDA's conclusion in Section "7.R.2 Appropriateness of the developmental strategy with a bridging approach and the validity of bridging" in Review Report (1), i.e., it is possible to extrapolate foreign clinical data from Foreign Studies 301 and 302 to Japanese patients with PD to evaluate the efficacy of opicapone.

1.2 Indication

The expert advisors supported the PMDA's conclusion in Section "7.R.5 Indication" in Review Report (1), including the correction of "levodopa-containing formulations" to "levodopa/carbidopa or levodopa/benserazide hydrochloride" so that opicapone is not administered with other COMT inhibitors by mistake.

1.3 Dosage and administration

(a) Dosing method

The expert advisors supported the PMDA's conclusions in Sections "6.R.2 Food effect and dose timing of opicapone" and "7.R.6 Dosage and administration" in Review Report (1), including that on the need of a cautionary statement advising that opicapone be taken ≥1 hour before or after a meal in the "Precautions Concerning Dosage and Administration" section of the package insert. The expert advisor further commented that additional necessary measures should preferably be advised for patients who cannot necessarily take opicapone at bedtime (i.e., bedtime dosing is not recommended).

(b) Dosage

The expert advisors supported PMDA's conclusion on the appropriateness of the recommended dose of 25 mg for Japanese patients with PD based on the regional difference in PK and efficacy and safety evaluation results from Studies 02, 301, and 302. Meanwhile, in terms of the recommended dose in Japan, which is half the recommended overseas dose level, and on the decision not to include dose increase option in the "Dosage and Administration" section, expert advisors commented that healthcare professionals should be appropriately informed of the factors behind the regional differences in opicapone exposure and adequate efficacy obtained at opicapone 25 mg in Japanese patients regardless of body weight or other patient characteristics.

Based on the above discussions at the Expert Discussion, the best recommended opicapone dose timing and relevant cautionary advice were discussed again. PMDA concluded that it is appropriate to describe in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as presented below. Information including the results of investigation on the differences in the PK of opicapone between Japanese and non-Japanese populations should be provided to healthcare professionals via the package insert and information materials.

Dosage and Administration

Opicapone is used in combination with levodopa/carbidopa or levodopa/benserazide hydrochloride. The usual adult dosage is 25 mg of opicapone administered orally once daily ≥1 hour before or after the administration of levodopa/carbidopa or levodopa/benserazide hydrochloride and ≥1 hour before or after a meal.

Precautions Concerning Dosage and Administration

(Omitted)

(3) Opicapone should be administered at a fixed appropriate time (such as bedtime) daily taking into consideration the patient's lifestyle, the dose timing of levodopa-containing formulation, etc.

1.4 Pharmacokinetic interactions

After the Review Report (1) was prepared, the applicant submitted results from pharmacokinetic interaction studies of opicapone, which were conducted in Europe in [redacted] 20[redacted]. The studies provided the grounds for revising the package insert of opicapone. The results of each study are shown below.

(a) Quinidine (Study [redacted]-1707, CTD 5.3.3.4-20 [reference data])
Non-Japanese healthy adults (n = 18) received a single oral dose of opicapone 50 mg under fasted conditions alone or 1 hour after a single oral dose of quinidine 600 mg. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of opicapone administered following quinidine to those of opicapone administered alone were 0.70 [0.60, 0.82] and 0.69 [0.55, 0.86], respectively.

(b) Repaglinide (Study [redacted]-1708, CTD 5.3.3.4-19 [reference data])
Non-Japanese healthy adults (n = 17) received a single oral dose of repaglinide 0.5 mg or oral doses of opicapone 50 mg once daily for 13 days that were followed by a single oral dose of opicapone 50 mg administered in combination with repaglinide 0.5 mg under fasted conditions. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of repaglinide coadministered with opicapone to those of repaglinide administered alone were 0.93 [0.82, 1.05] and 1.00 [0.93, 1.08], respectively.

The applicant's explanation about the appropriateness of cautionary advice in the package insert based on the clinical study results:
Because the *in vitro* study demonstrated that opicapone is a substrate for P-gp [see Section "6.2.1.6 Transporters"], the effect of quinidine, a typical P-gp inhibitor, on the PK of opicapone was investigated in Study [redacted]-1707. The C_{max} and $AUC_{0-\infty}$ of opicapone decreased when coadministered with quinidine as compared with opicapone administered alone. Although how the combination use of opicapone with quinidine could decrease opicapone exposure remains unclear, it is appropriate to provide cautionary advice in the package insert on the use of opicapone with quinidine.

An *in vitro* study indicated that opicapone and BIA 9-1103 inhibit CYP2C8 [see Section "6.2.1.4 Enzyme inhibition"]. In Study BIA-91067-115, the C_{max} and $AUC_{0-\infty}$ of repaglinide, a typical CYP2C8 substrate, tended to increase when coadministered with opicapone [see Section "6.2.6.1.2 Repaglinide"]. However, the study used a formulation with bioavailability of approximately 50% of that of the commercial formulation overseas to investigate the effect on the PK of repaglinide following a single dose of repaglinide coadministered with opicapone 25 mg. Therefore, in Study [redacted]-1708, aiming to simulate more actual use of opicapone in the clinical setting, the effect of a single dose of repaglinide coadministered with opicapone 50 mg on the PK of repaglinide was investigated after multiple doses of opicapone using the 50 mg capsule formulation used in the foreign phase III studies (Foreign Studies 301 and 302). The coadministration of repaglinide with opicapone had no effect on the C_{max} and $AUC_{0-\infty}$ of repaglinide, showing inconsistency with Study BIA-91067-115. The reason is unclear why only Study BIA-91067-115 showed the trend toward increased repaglinide exposure following the dose coadministered with opicapone. However, as mentioned above, given that Study [redacted]-1708 was conducted in the setting more similar to the actual clinical use of opicapone than in Study BIA-91067-115, opicapone is unlikely to affect the PK of CYP2C8 substrates based on the results of Study [redacted]-1708, and cautionary advice on the coadministration of opicapone with CYP2C8 substrates is not necessary.

PMDA's view:

Based on the results of Study [redacted]-1707, it is appropriate to provide cautionary advice on the coadministration of opicapone with quinidine via the package insert, as explained by the applicant. It is also reasonable to place importance on the results of Study [redacted]-1708 that was conducted in the setting more similar to the actual clinical use of opicapone, in association with the coadministration of opicapone with CYP2C8 substrates. Based on the results of Study [redacted]-1708, the applicant's explanation about the needlessness of cautionary advice on the coadministration of opicapone with CYP2C8 substrates is appropriate.

1.5 Risk management plan (draft)

In view of the discussions in Section "7.R.7 Post-marketing investigations" in Review Report (1), and taking into account the comments from the Expert Discussion, PMDA concluded that the risk management plan (draft) for opicapone should include the safety specification presented in Table 56, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 57 and specified use-results survey presented in Table 58.

Table 56. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Dyskinesia • Hallucination, hallucination visual, hallucination auditory, delirium • Orthostatic hypotension	• Somnolence, sudden onset of sleep • Neuroleptic malignant syndrome • Impulse-control disorders • Hepatic dysfunction	None
Efficacy specification		
None		

Table 57. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	• Disseminate information obtained via early post-marketing phase vigilance • Prepare written materials for healthcare professionals to disseminate information • Prepare written materials for patients and families to disseminate information

Table 58. Outline of specified use-results survey (draft)

Objective	Investigation on the occurrence of dyskinesia, hallucination, hallucination visual, hallucination auditory, delirium, and orthostatic hypotension in the clinical setting and identification of adverse reactions (adverse events) in long-term treatment
Survey method	Central registration
Population	Patients with PD treated with levodopa-containing formulations experiencing wearing-off
Observation period	52 weeks
Planned sample size	250 patients (safety analysis set)
Main survey item	Dyskinesia, etc.

1.6 Other

The applicant informed that their planning for a stable supply [redacted] still remained uncompleted due to the impact of [redacted]. At that time, PMDA considered that the applicant were not able to assure stable supply of opicapone that would influence its marketing approval in Japan. However, [redacted], applicant explained that the issue of [redacted] had been solved. In response, PMDA made a final decision on the approval of the product.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following error at some of the study sites. Although it did not substantially affect the evaluation of the entire study, the error was notified to the head of the study sites as a finding requiring corrective action:

Finding requiring corrective action

Study sites

• Protocol deviation (non-adherence to the rules on prohibited concomitant drugs)

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration presented below, with the following approval conditions. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug substance is classified as a poisonous drug, and the drug product is classified as powerful drug.

Indication

Improvement of end-of-dose motor fluctuations (wearing-off phenomenon) in patients with Parkinson's disease by combination use with levodopa/carbidopa or levodopa/benserazide hydrochloride

Dosage and Administration

Opicapone is used in combination with levodopa/carbidopa or levodopa/benserazide hydrochloride. The usual adult dosage is 25 mg of opicapone administered orally once daily at least 1 hour before or after the administration of levodopa/carbidopa or levodopa/benserazide hydrochloride and at least 1 hour before or after a meal.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

APD 30	Action potential duration at 30% repolarization
APD 60	Action potential duration at 60% repolarization
APD 90	Action potential duration at 90% repolarization
APT	Action potential triangulation
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve of the analyte in plasma
$AUC_{0-\infty}$	AUC from time zero to infinity
AUC_{0-t}	AUC from time zero to time t
AUC_{0-last}	AUC from time zero to the last quantifiable concentration
AUEC	Area under the effect-time curve
$AUEC_{0-24h}$	AUEC up to 24 hours post-dose
$AUEC_{last}$	AUEC from time zero to the last quantifiable concentration
BE	Bioequivalence
BIA 9-1067	2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide
BIA 9-1079	5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-1,2,4-oxadiazol-5-yl]-3-nitrobenzene-1,2-diol
BIA 9-1100	2,5-dichloro-3-[5-(4-hydroxy-3-methoxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl]-4,6-dimethylpyridine 1-oxide
BIA 9-1101	4-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-1,2,4-oxadiazol-5-yl]-2-methoxy-6-nitrophenol
BIA 9-1103	5-[3-(2,5-dichloro-4,6-dimethyl-1-oxo-1λ^5-pyridin-3-yl)-1,2,4-oxadiazol-5-yl]-2-hydroxy-3-nitrophenyl hydrogen sulfate
BIA 9-1104	5-[3-(2,5-dichloro-4,6-dimethyl-1-oxo-1λ^5-pyridin-3-yl)-1,2,4-oxadiazol-5-yl]-2-methoxy-3-nitrophenol
BIA 9-1106	5-[3-(2,5-dichloro-4,6-dimethyl-1-oxo-1λ^5-pyridin-3-yl)-1,2,4-oxadiazol-5-yl]-2-hydroxy-3-nitrophenyl β-D-glucopyranosiduronic acid
C_{max}	Maximum observed concentration
CMC	Carboxymethylcellulose
COMT	Catechol-*O*-methyltransferase
CQA	Critical quality attribute
CK	Creatine phosphokinase
CI	Confidence Interval
CPP	Critical process parameter
C_{24h}	Plasma concentration 24 hours post-dose
ED_{50}	Half maximal effective concentration
DCI	Dopa-decarboxylase inhibitor
DOPAC	3,4-dihydroxyphenylacetic acid
DMSO	Dimethyl sulfoxide
E_{max}%	Maximum S-COMT inhibition
E_{min}%	Minimum S-COMT inhibition
FAS	Full Analysis Set
GC	Gas chromatography
HDPE	High density polyethylene
hERG	Human ether-à-go-go related gene
HPLC	High performance liquid chromatography
HPLC-ED	High performance liquid chromatography - electrochemical detection
HPMC	Hydroxypropyl methylcellulose
HVA	Homovanillic acid

IC_{50}	Half maximal inhibitory concentration
ICH M7 Guidelines	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use M7 Guidelines: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/ELD Notification No. 1110-3, dated November 10, 2015)
ICH Q1E Guidelines	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q1E Guidelines: Evaluation for Stability Data (PFSB/ELD Notification No. 0603004, dated June 3, 2003)
INR_{max}	Maximum international normalised ratio
$INRAUC_{144h}$	AUC for international normalised ratio (prothrombin time) up to 144 hours post-dose
IR	Infrared absorption spectroscopy
K_i	Inhibition constant
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
MAO	Monoamine oxidase
MAO-B	Monoamine oxidase-B
MB-COMT	Membrane-bound COMT
MC	Methylcellulose
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mRNA	Messenger ribonucleic acid
MS	Mass spectrometry
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NMR	Nuclear magnetic resonance spectroscopy
OATP	Organic anion transporting polypeptide
3-OMD	3-*O*-Methyldopa
$P_{app\ A\rightarrow B}$	Apparent permeability coefficient A→B
$P_{app\ B\rightarrow A}$	Apparent permeability coefficient B→A
PAPS	3'-phosphoadenosine-5'-phosphosulfate
PCR	Polymerase chain reaction
PD	Parkinson's disease
[redacted]	[redacted]
PDE	Phosphodiesterase
PE	Polyethylene
PK	Pharmacokinetic/pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Polypropylene
PPK	Population pharmacokinetic/ pharmacokinetics
PPMRS	Primate Parkinsonism Motor Rating Scale
PPS	Per protocol set
PT	Prothrombin time
PTP	Press through packaging
[redacted]	[redacted]
QbD	Quality by Design
QTcI	Individually corrected QT interval
SAM	S-(5'-adenosyl)-L-methionine p-toluenesulfonate salt
S-COMT	Soluble COMT
Study 301	Study BIA-91067-301
Study 302	Study BIA-91067-302

Study 02	Study ONO-2370-02
SULT	Sulfotransferase
The Guideline for Bioequivalence Studies for Formulation Changes	The Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms (PMSB/ELD Notification No. 67, dated February 14, 2000; partial revision in PFSB/ELD Notification No. 0229-10)
t_{max}	Time to reach C_{max}
TSPO	Translocator protein
UDPGA	Uridine 5'-diphosphoglucuronic acid
UGT	UDP-glucuronosyltransferase
UKPDS	United Kingdom Parkinson's Disease Society
UV-A	Ultraviolet A
UV-B	Ultraviolet B
UV/VIS	Ultraviolet-visible spectroscopy