CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

NDA Number	212489
Link to EDR	\\cdsesub1\evsprod\nda212489
Submission Date	04/26/2019
Submission Type	505(b)(1) NME NDA (Standard Review)
Brand Name	ONGENTYS
Generic Name	opicapone
Dosage Form/Strength and Dosing Regimen	Capsules: 25 mg and 50 mg 50 mg administered orally once daily at bedtime
Route of Administration	Oral
Proposed Indication	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's Disease experiencing "OFF" episodes
Applicant	Neurocrine Biosciences, Inc. (NBI)
Associated IND	IND (b) (4)
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OCP Final Signatory	Mehul Mehta, Ph.D.

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1. EXECUTIVE SUMMARY

Neurocrine Biosciences, Inc. (NBI) submitted a new drug application (NDA) seeking approval for ONGENTYS® (opicapone, BIA-91067) 25 mg and 50 mg capsules as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "OFF" episodes. Opicapone (OPC) is a reversible peripheral catechol-O-methyltransferase (COMT) inhibitor. In the presence of a peripheral dopamine decarboxylase inhibitor (DDCI) such as carbidopa, COMT becomes the major peripheral metabolizing enzyme for levodopa, catalyzing its conversion to 3-O-methyldopa (3-OMD). In humans, opicapone inhibits the COMT enzyme in peripheral tissues, resulting in an increase in overall exposure to levodopa and a decrease in exposure to 3-OMD.

The clinical development program of OPC included 38 studies: 34 Phase 1 studies, two Phase 2 studies, and two Phase 3 studies in subjects with PD (see Section 4.3 for more details; Table 10). The clinical pharmacology studies characterized: (1) the effect of different dosing regimens of OPC on levodopa exposure, (2) the effect of intrinsic and extrinsic factors on the plasma exposure of opicapone, (3) assessment of QT prolongation through a thorough QT (TQT) study, and (4) PK bridging between the to-be-marketed (TBM) formulation and the clinical trial formulations.

The primary evaluation of efficacy and safety of opicapone for the proposed indication is from two Phase 3 studies, which assessed the effectiveness of OPC in reducing OFF-time in patients with idiopathic PD and motor fluctuations when administered with existing treatment of levodopa plus a DDCI. OPC was administered at doses of 5 mg (Study BIA-91067-301 only), 25 mg, and 50 mg. Both studies showed a statistically significant decrease in absolute OFF-time in subjects treated with OPC 50 mg. Subjects treated with either OPC 5mg or 25mg failed to reach statistical significance.

The primary objectives of this review are to evaluate:

1. the acceptability of the proposed general dosing recommendation,
2. the need for dose adjustments based on intrinsic and extrinsic factors, and
3. the acceptability of the PK bridging between the Phase 3 clinical trial formulation and the to-be-marketed formulation.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted under NDA 212489 and recommends approval of opicapone (ONGENTYS) as an adjunctive therapy to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing OFF episodes.

Key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness of OPC is from two Phase 3 studies, BIA-91067-301 and BIA-91067-302. These were randomized, double-blind, placebo-controlled (both studies) and active-controlled (BIA-91067-301) studies to assess the effectiveness of OPC in reducing the OFF-time in patients with idiopathic PD treated with levodopa plus a DDCI. OPC was administered at doses of 5 mg (Study BIA-91067-301 only), 25 mg, and 50 mg. Both studies showed a statistically significant decrease in OFF time in subjects treated with OPC 50 mg.
General dosing instructions	50 mg taken orally once daily at bedtime, 1 hour away from food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose adjustments is needed for the following intrinsic factors: • Moderate (Child-Pugh B) hepatic impairment: the recommended dose of ONGENTYS is 25 mg orally once daily. • Severe (Child-Pugh C) hepatic impairment: Avoid use ONGENTYS. • End-Stage Renal Disease (CLcr <15 mL/min): Avoid use ONGENTYS.
Labeling	The review team recommends changes to the USPI to reflect the recommended dose optimizations based on intrinsic and extrinsic factors described above.
Bridge between the to-be-marketed and clinical trial formulations	The bridge between the to-be marketed capsules and clinical trial capsules is acceptable. Four formulations were used during the clinical development program of OPC: non-micronized, micronized, registrational, and the to-be-marketed formulations. The non-micronized formulation was used in the early Phase 1 studies as well as in the Phase 2 studies. The micronized formulation was used in some Phase 1 studies as well as in the pivotal Phase 3 trials. The registrational formulation is the commercial-scale lots of the micronized formulation. The required PK bridging between the micronized formulation used in Phase 3 and the registrational formulation was demonstrated in Study BIA-91067-119. The proposed to-be-marketed formulation in US is

	identical to the registrational formulation, with a slightly different color for capsules. The Office of Study Integrity and Surveillance (OSIS) conducted a routine site inspection for the pivotal PK bridging study BIA-91067-119 and recommended that the data from study BIA-91067-119 are not reliable to support a regulatory decision. This was because of the non-availability of reserve samples for the test and reference products at the study site. There were no other issues related to study conduct or bioanalysis in the inspection report. The study site reported to OSIS that the reserve samples were discarded after opicapone received European Union Marketing Authorization in 2016 and that they followed EU regulations (Ref. Surveillance inspection of Biotrial Rennes, Rennes, France Review Report in DARRTS dated 2/26/2020). The documentation of the test and reference product administration in the study was inspected by OSIS and was also considered acceptable. Since the only issue is related to independent verification of the test (registrational formulation) and reference (Phase 3 formulation) products used in the PK bridging study the review team relied on PK data from other Phase 1 studies that used either the Phase 3 clinical trial formulation or the registrational formulation to independently verify the reliability of Study BIA-91067-119. In general, with cross-study comparisons, the PK results from these studies were in agreement with the PK bridging study BIA-91067-119. In addition, EMA had considered Study BIA-91067-119 during the review and subsequent approval of opicapone in 2016. Based on these, the review team concluded that the study BIA-91067-119 is acceptable.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action:

Opicapone is a reversible peripheral COMT inhibitor. In the presence of a peripheral DDCI (e.g. carbidopa), COMT becomes the major peripheral metabolizing enzyme for levodopa, catalyzing its conversion to 3-OMD. In nonclinical models, administration of opicapone with levodopa/DDCI results in an increase in systemic and brain levodopa concentrations. In humans, opicapone inhibits the COMT enzyme in peripheral tissues, resulting in an increase in overall exposure to levodopa and a decrease in exposure to 3 -OMD.

Absorption:

Following 50 mg dose of ONGENTYS, the median time to C_{max} (T_{max}) is 2 hours (Range: 1-4 hours). The geometric mean (CV%) of C_{max} is 803 (40%) ng/mL.

Food Effect: The effect of a moderate fat/calorie meal on OPC PK was investigated after multiple doses of 50 mg OPC micronized capsule formulation administered once daily in Study BIA-91067-128. OPC C_{max} and AUC_{last} values decreased by 62% and 31%, respectively, and the median T_{max} was delayed by 4 hours following administration under fed relative to fasted conditions. Therefore, OPC should not be taken with food.

Distribution:

In vitro studies indicated that binding of OPC and its major metabolite BIA 9-1103 (inactive sulfate conjugate) to human plasma proteins is high (>99%) and concentration independent. When OPC and BIA 9-1103 were co-incubated in vitro with warfarin, diazepam, digoxin, or tolbutamide, no mutual displacement from plasma protein binding sites was observed for any of the compounds. Likewise, there was no binding interaction seen between OPC and BIA 9-1103.

Metabolism:

Results from an ADME study (BIA-91067-130) showed that OPC is eliminated mainly through metabolism, forming a major inactive sulfate conjugate (BIA 9-1103). This sulfate conjugate is believed to be mediated by SULT1A1 based on in vitro studies.

Other minor metabolic pathways include glucuronidation, methylation (by COMT), reduction, and glutathione conjugation. BIA 9-1079 (reduced pyridine N-oxide), BIA 9-1104 (4-O-methyl OPC), and BIA 9-5049 (cysteine + methyl conjugate) are active metabolites of OPC. However, exposures of these metabolites were very low[1,2,3].

Excretion:

The elimination half-life of OPC is approximately 1-2 hours. Following administration of a single dose of ^{14}C-labeled OPC, 96% of the administered dose of radioactivity was recovered. The main

[1] In Study BIA-91067-130, plasma concentrations of BIA 9-1079 were below the limit of quantification (BLQ; 10 ng/mL), with the exception of the 8-hour sample collected from 1 subject where the concentration of BIA 9-1079 was 11.1 ng/mL. Similarly, in Study BIA-91067-126, BIA 9-1079 plasma concentrations were found to be BLQ for the all timepoints and at the tested dose range (5 to 50 mg OPC).

[2] In Study BIA-91067-126, BIA 9-1104 plasma concentrations were found to be BLQ for the majority of the timepoints and at the tested dose range (5 to 50 mg OPC) at Day 10. This is expected as this metabolite is formed by COMT.

[3] In study BIA-91067-130, BIA 9-5049 represented an average of 3.72% of circulating radioactivity. While the applicant did not determine the exposure of BIA 9-5049 in plasma and urine in this study, this metabolite is downstream of BIA 9-1104 (representing on an average 6.6% of circulating radioactivity) which is formed by COMT. Therefore, the exposure of this metabolite is expected to be BLQ at steady state and the clinical relevance of this metabolite is considered low.

excretion route was feces, accounting for approximately 70% of the administered radioactivity. The remainder of the radioactivity was excreted in urine (5%) and via expired air (20%). About 22.3% of the radioactive dose was recovered as unchanged OPC in feces. Only traces (<1%) of the unchanged OPC was detected in urine. Most of the radioactivity was eliminated within 144 hours post-dose.

Dose proportionality:

The PK of single doses of the to-be-marketed formulation was approximately dose-proportional in healthy subjects over a clinically relevant dose range of 25 to 50 mg (Study BIA- 91067-119).

Special Populations:

Hepatic Impairment:

Following a single dose of 50 mg OPC, the geometric mean ratios of C_{max} and AUC_{inf} were 34% and 35% higher in subjects with mild hepatic impairment (Child-Pugh score A) compared to matched healthy subjects with normal hepatic function (Study NBI-OPC-1705). On the other hand, following a single dose of 50 mg OPC, the geometric mean ratios of OPC C_{max} and AUC_{inf} in subjects with moderate hepatic impairment (Child-Pugh score B) were 89% and 84% higher compared to the matched healthy subjects with normal hepatic function (Study BIA-91067-106). Please refer to Section 3.3.3 for details.

Renal Impairment:

Renal route of elimination plays only a minor role in the clearance of OPC. In an ADME study (BIA-130), only about 5% of the total administered radioactivity was recovered in urine, and most radioactivity (~70%) was found in the fecal samples. A clinical pharmacology study to evaluate the impact of renal impairment on the pharmacokinetics of OPC was not conducted. Instead, a population PK approach was used to assess the impact of renal impairment on OPC exposure (Report 2018-CP-198) and renal function (as measured by creatinine clearance using CG equation) did not have a statistically significant effect the clearance of OPC in patients with mild and moderate renal impairment (creatinine clearance > 30 mL/min). Patients with severe renal impairment or ESRD (creatinine clearance ≤ 30 mL/min) were not studied. Please refer to Section 3.3.3 for details.

Age, Race, Sex, and Body Weight:

Study BIA-91067-105 evaluated the effect of age on the pharmacokinetics of OPC. The geometric mean ratios for OPC C_{max} and AUC_{last} following single and multiple doses of OPC were 9% to 28% higher in elderly subjects (age≥ 65 years) compared to young subjects (age 18-40 years).

The geometric mean ratios for C_{max} and AUC_{inf} following the first dose of 50 mg OPC were ~15% and 26% higher in healthy Japanese subjects compared to matched healthy Caucasian

participants. Consistently, the geometric mean ratios for the steady-state C_{max} and AUC were ~20% higher in healthy Japanese subjects compared to matched healthy Caucasian subjects (Study BIA-91067-126).

The impact of body weight on exposure was evaluated using population PK (Pop-PK) analysis. This analysis also included race, age and sex and was shown to have no significant impact on OPC systemic exposure. Please refer to Section 3.3.3 and Section 4.2 for details.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose is 50 mg once daily taken orally at bedtime, 1 hour away from food as done in the pivotal Phase 3 study, BIA-91067-302.

2.2.2 Therapeutic individualization

Therapeutic individualization is necessary only for the following intrinsic factors.

Hepatic Impairment:

Two clinical studies in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment showed that the overall exposure (AUC_{inf}) of OPC increased by ~35%, and ~84%, respectively, relative to matched healthy controls. No dose adjustments are required in subjects with mild hepatic impairment. Patients with moderate hepatic impairment should be advised to use OPC 25 mg. Patients with severe (Child-Pugh C) hepatic impairment were not studied during the clinical development of OPC. Avoid use of opicapone in patients with severe hepatic impairment.

Renal Impairment:

Pop-PK analysis based on pooled data from clinical studies was used to evaluate the effect of renal impairment based on estimated creatinine clearance (CLcr) using the Cockcroft-Gault (CG) equation. Renal impairment did not result in a significant difference in the pharmacokinetics of opicapone in patients with mild or moderate renal impairment (CLcr 30-89 mL/min) relative to those with normal renal function (CLcr >90 mL/min). Patients with severe renal impairment or ESRD (CLcr<30 mL/min) have not been studied. Since renal impairment is a minor route of elimination (<1% of unchanged opicapone eliminated in urine) and no changes in exposures were observed for the mild and moderate renal impairment group, no dose adjustment is recommended in patients with severe renal impairment (CLcr 15-29 mL/min) as well. However, if there any tolerability issues, discontinue the use of opicapone. Avoid use of opicapone in patients with ESRD (CLcr<15 mL/min).

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling concepts to be included in the final package insert.

- The recommended dose of ONGENTYS™ is 50 mg capsules once daily administered at bedtime, 1 hour away from food.
- Dose adjustment is not required for mild hepatic impairment (Child-Pugh A), mild, moderate or severe renal impairment (CLcr ≥15 mL/min), or based on demographic factors such as age, sex, race, and body weight.
- In patients with moderate hepatic impairment (Child-Pugh B), use 25 mg dose.
- Avoid use of ONGENTYS in patients with severe hepatic impairment (Child-Pugh C)
- Avoid use of ONGENTYS in patients ESRD (CLcr<15 mL/min)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Neurocrine Biosciences, Inc. (NBI) has submitted a 505(b)(1) New Drug Application (NDA) for ONGENTYS® (opicapone; OPC) 25 mg and 50 mg capsules. ONGENTYS, a new molecular entity, is a reversible peripheral COMT inhibitor developed as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing OFF episodes.

ONGENTYS was developed by the product innovator, BIAL – Portela & Ca, S.A. (BIAL). In February 2017, NBI and BIAL entered into an exclusive licensing agreement for the development and commercialization of ONGENTYS in North America. A European Union Marketing Authorization was granted to BIAL-Portela & Ca, S.A. for ONGENTYS® in June 2016; a Marketing Authorization was granted in Switzerland in April 2018. ONGENTYS® 50 mg has been marketed in Germany and the United Kingdom since October 2016, and in Spain since May 2017.

The clinical development program of OPC comprised of 38 studies: 34 Phase 1 studies, 2 Phase 2 studies, and 2 Phase 3 studies (double-blind with open-label extension) in subjects with PD. Key design features for these studies are summarized in Section 4.3.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	ONGENTYS is a reversible peripheral COMT inhibitor. In the presence of a peripheral DDCI (e.g. carbidopa), COMT becomes the major peripheral metabolizing enzyme for levodopa, catalyzing its conversion to 3-OMD. In humans, ONGENTYS inhibits the COMT enzyme in peripheral tissues, resulting in an increase in overall exposure to levodopa and a decrease in exposure to 3-OMD.
Active Moieties	OPC is the active moiety. No clinically relevant active metabolites were reported for OPC.
QT Prolongation	No significant QTc prolongation effect of OPC (50 mg and 800 mg) was detected in a TQT study BIA-91067-111 (See QT-IRT Review).
General Information	
Bioanalysis	The concentrations of OPC in human plasma were measured using a validated LC-MS/MS method. Please refer to Section 4.1 for details.
Healthy Volunteers vs. Patients	PK is similar between PD patients and healthy subjects. Please refer to Section 4.2 for more details.
Dose Proportionality	Non-micronized formulation (used in Phase 1 and Phase 2 studies): 10 to 50 mg single dose (Study BIA 91067-101). Micronized formulation (used in some Phase 1 and Phase 3 studies): 25 to 50 mg single dose (Study BIA-91067-121) and 5 to 50 mg once daily multiple dose range (Study BIA-91067-126). To-be-marketed formulation: 25 to 50 mg single dose range (Study BIA-91067-119).
Accumulation	No accumulation is noted after repeated once daily dosing. Steady state is achieved within one day.
Variability	The %CV of C_{max} and AUC_{inf} following single dose OPC 50 mg to-be-marketed formulation were 40% and 45%, respectively (Study BIA-91067-119). The %CV of C_{max} and AUC_{inf} following single dose OPC 25 mg (to-be-marketed) were 43%, and 39%, respectively.
Absorption	
Bioavailability	The absolute oral bioavailability of OPC was not determined.
T_{max}	Following 50 mg dose of ONGENTYS, the median time to C_{max} (T_{max}) value is 2 hours (1-4 hours).
Food effect (moderate fat/moderate calorie meal) GMR relative to	OPC C_{max} and AUC_{last} values decreased by 62% and 31%, respectively, following administration under fed relative to fasted conditions.

fasted state after multiple dosing	
Distribution	
Volume of Distribution	Mean (%CV) single dose Vd/F values ranged from 38.6 (33) L in elderly subjects to 45.4 (72) L in nonelderly subjects (Study BIA-91067-105).
Plasma Protein Binding	>99% (at concentrations ranging from 0.3 to 30 µg/mL).
Substrate transporter systems	OPC is a substrate for P-gp, BCRP, MRP2, OATP1B3, and OATP2B1 in in-vitro transporter assays.
Elimination	
Mean Terminal Elimination half-life	Approximately 1-2 hours
Metabolism	
Primary metabolic pathway(s) [*in vitro*]	SULT1A1 is the primary enzyme involved in the metabolism of OPC.
Inhibitor/Inducer	• In human hepatic microsomes OPC and its major sulfate metabolite, BIA 9-1103 caused <30% inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6 and CYP2E1 activities at the highest concentrations tested (10 µg/mL OPC, 30 µg/mL BIA 9-1103) • Time-dependent inhibition was not observed for either OPC or BIA 9-1103 with any of the CYP isoforms evaluated • OPC and BIA 9-1103 are not inducers to CYP1A, CYP2B6, and CYP3A4 in human hepatocytes. • OPC and BIA 9-1103 inhibited OAT1, OAT3, OATP1B1, and OATP1B3, with IC50 values of 9.18, 4.36, 0.45, and 1.40 µg/mL for OPC, and 13.20, 2.55, 2.80, and 7.51 µg/mL for BIA 9-1103, respectively • CYP-mediated clinically relevant drug interactions perpetrated by OPC or its metabolite BIA 9-1103 are considered unlikely when taking into consideration the relevant free (unbound) C_{max} following 50 mg dosing for OPC and its major metabolite. In addition, clinical studies demonstrated no clinically relevant interaction with warfarin (CYP2C9 substrate) or repaglinide (CYP2C8 and OATP1B1 substrate). As no clinical drug interaction was observed with repaglinide, a sensitive OATP1B1 substrate, it can be presumed that there is a low potential for OPC drug interactions with other transporters that had higher IC50 values

Excretion	
Primary excretion pathways	OPC is mainly cleared through metabolism. Fecal excretion accounted for about 70% of the dose while recovery from urine was about 5%. About 22.3% of the radioactive dose was recovered as unchanged OPC in feces. Only traces (<1%) of the unchanged OPC was detected in urine.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of effectiveness of OPC for the sought indication is from two Phase 3 studies, BIA-91067-301 and BIA-91067-302. These are randomized, double-blind, placebo-controlled (both studies) and active-controlled (BIA-91067-301) studies to assess the effectiveness of OPC in reducing the OFF-time in patients with idiopathic PD and motor fluctuations after 14 to 15 weeks of the double-blind period. Study BIA-91067-301 assessed the efficacy and safety of 5 mg, 25 mg, and 50 mg doses of OPC, while Study BIA-91067-302 included only 25 mg and 50 mg doses of OPC. Subjects from both studies were allowed to continue in a 1-year open-label extension period.

Both Phase 3 studies included patients aged 30 to 83 years, had a diagnosis of idiopathic PD for at least 3 years with a disease severity of Stage 1 to 3 (based on the modified Hoehn and Yahr scale) during ON state, treated with levodopa/DDCI for at least 1 year with clear clinical improvement, on a stable regimen of levodopa/DDCI and other PD drugs for at least 4 weeks before screening, had signs of "wearing-off" phenomenon (end-of-dose deterioration) for at least 4 weeks before screening despite optimal PD therapy[4], with average total daily OFF-time while awake of at least 1.5 hours (excluding pre-first dose OFF)[5]. In Study BIA-91067-301, a total of 600 subjects were randomized in the double-blind period: 121 to placebo, 122 to entacapone, 122 to opicapone 5 mg, 119 to opicapone 25 mg, and 116 to opicapone 50 mg. In Study BIA-91067-302, a total of 427 subjects were randomized in the double-blind period: 144 subjects to placebo, 129 subjects to OPC 25 mg and 154 subjects to OPC 50 mg. Both studies used the micronized capsule formulation of OPC.

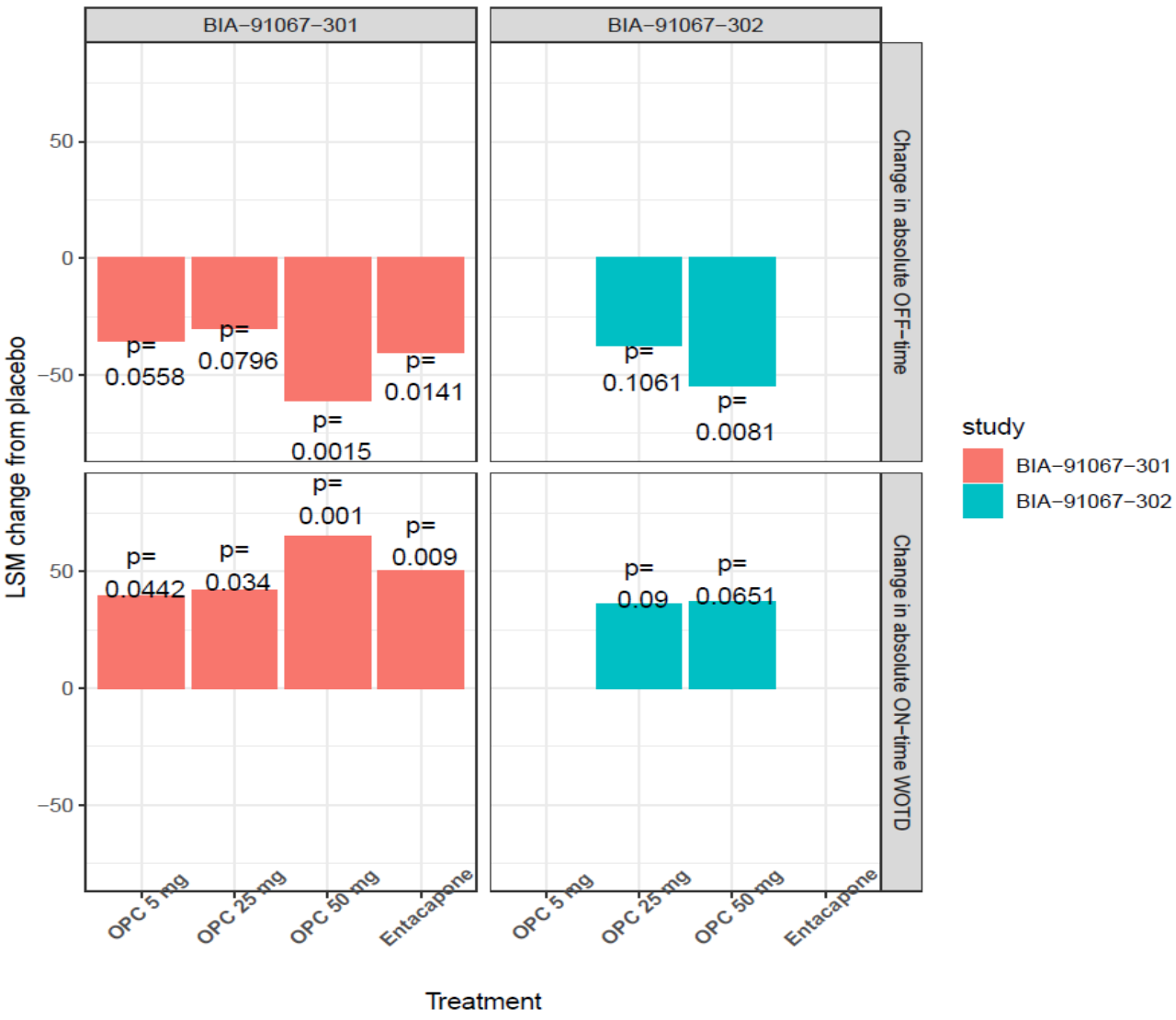
The prespecified primary efficacy endpoint for Studies BIA-91067-301 and BIA-91067-302 was the change from baseline in absolute OFF-time at the end of the double-blind period (Visit 7). The key secondary efficacy endpoints for both studies were OFF-time responders (1 hour or more reduction in absolute OFF-time from baseline to endpoint) and ON-time responders (1 hour or more increase in absolute ON-time from baseline to endpoint). In addition, the applicant

[4] based on the Investigator's judgment
[5] based on patient-recorded PD diaries

evaluated ON-time without troublesome dyskinesia as a key secondary endpoint in the pooled efficacy analysis (for more information, please refer to the clinical review).

Figure 1 presents results of both Phase 3 studies for the change from baseline in absolute OFF-time at the end of the double-blind period and the change from baseline in ON-time without troublesome dyskinesia.

Figure 1. Change from Baseline in Absolute OFF-time (Upper) and Change from Baseline in ON-time Without Troublesome Dyskinesia (Lower) by Dose at the End of the Double-blind Period in Studies BIA-91067-301 and BIA-91067-302



Source: Figure generated by FDA reviewer from studies BIA-91067-301 and BIA-91067-3012. P-values represents the nominal P-values reported by the applicant

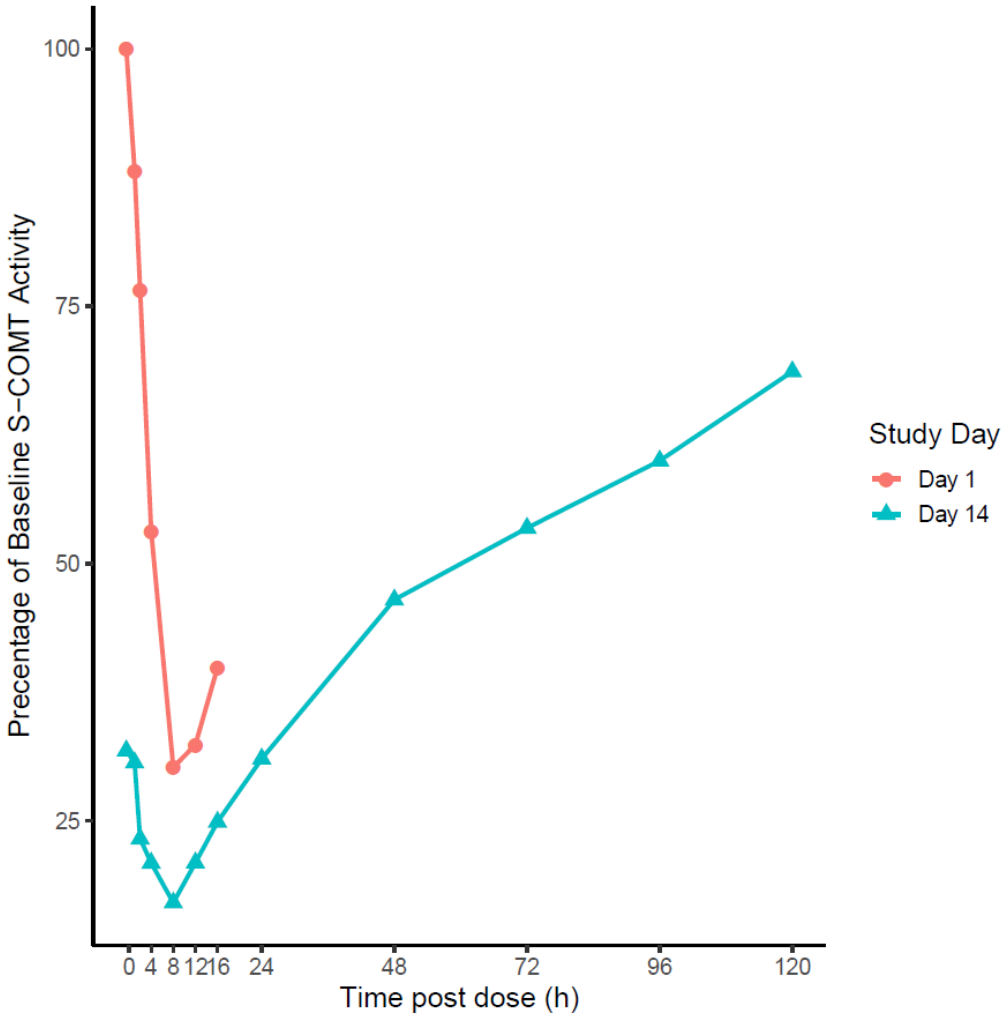
The applicant also conducted two Phase 2 studies in PD subjects treated with levodopa/DDCI (Studies BIA-91067-201 and BIA-91067-202) using OPC non-micronized formulation. Study BIA-91067-201 was a randomized, double-blind, placebo-controlled, crossover study that investigated the effect of single doses of 25, 50, and 100 mg OPC on the PK of levodopa/DDCI after simultaneous co-administration in PD patients (N=10). Study BIA-91067-202 was a randomized, double-blind, placebo-controlled, parallel-group study that investigated the effect of three dose levels of OPC: 5, 15, or 30 mg administered once daily (QD) in the morning for 21 to 28 days on the PK of levodopa/DDCI when OPC was administered 1 hour prior to levodopa/DDCI administration in PD patients (N=40). An increase in levodopa exposure was observed in PD patients with OPC. Consistently, a dose-dependent pharmacodynamic effect on S-COMT activity[6] was also observed in both studies. Moreover, an improvement in the motor function as assessed by daily OFF-time was observed in the multiple-dose Phase 2 study[7].

Moreover, the applicant conducted a Phase 1 PK/pharmacodynamic study in PD patients (Study NBI-OPC-1706). In this study, PD subjects (N=16) received 50 mg QD micronized OPC at bedtime for 14 days as adjunctive therapy to levodopa/carbidopa administered either every 3 hours (Q3H) or every 4 hours (Q4H). Peak S-COMT inhibition is observed at approximately 6 to 8 hours post-dose. There was more than 65% S-COMT inhibition that was sustained over the entire 24-hour dose interval and >35% S-COMT inhibition that was maintained 5 days following the last OPC dose (Figure 2). For both q3h and q4h levodopa dosing, once-daily OPC was associated with 43-44% increase in overall levodopa C_{max} and 62-94% increase in AUC_{last} (Figure 3).

[6] S-COMT activity was assessed by the amount of metanephrine (in pmol) formed by the action of S-COMT in washed erythrocytes on epinephrine, per milligram of hemoglobin in the sample, per hour. S-COMT activity inhibition was calculated as the percent change of the rate of formation of metanephrine from pre-dose to post-dose values

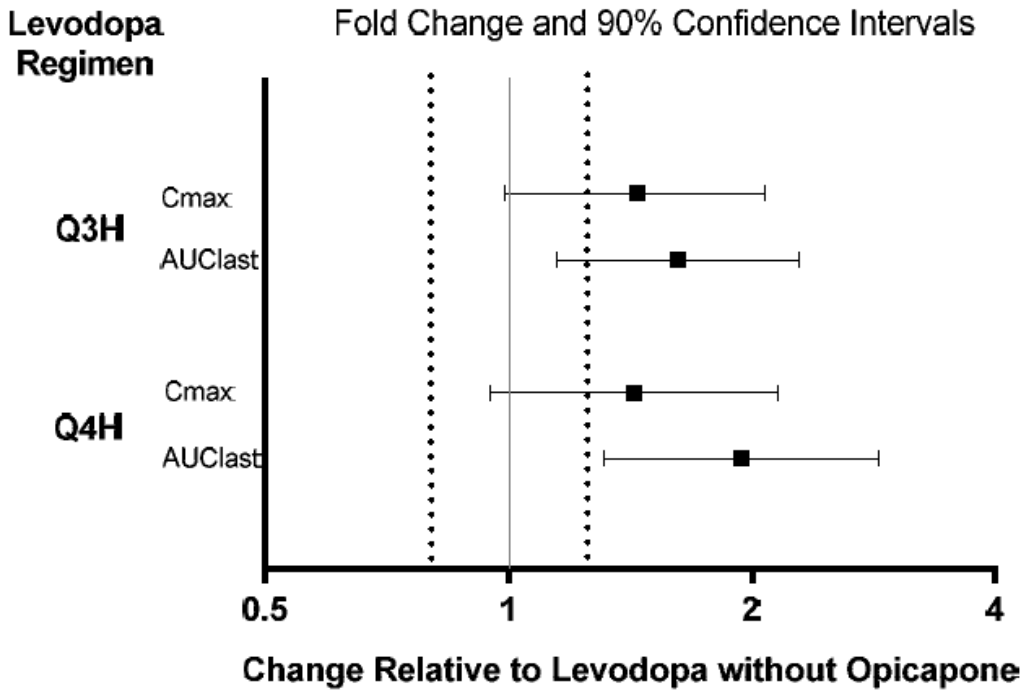
[7] Daily OFF-time was 359.4 minutes (5.99 hours) with OPC 5 mg QD, 278.8 minutes (4.65 hours) with 15 mg QD, and 298.3 minutes (4.97 hours) with 30 mg QD compared to 422.8 minutes (7.05 hours) with placebo.

Figure 2. Mean (SD) Percent Change from Baseline in S-COMT Inhibition Following Single (Day 1) and Multiple (Day 14) Doses of 50 mg QD Micronized OPC Administered 1 Hours Before Levodopa/Carbidopa (Study NBI-OPC-1706)



Source: Reviewer Analysis

Figure 3: Effect of 50 mg QD Micronized OPC Administered 1 Hours Before LD/Carbidopa on LD exposure (Study NBI-OPC-1706)



Source: Figure [redacted] (b) (4) based on Study NBI-OPC-1706 [redacted] (b) (4)

The Phase 1 clinical pharmacology studies in healthy volunteers also provide supportive evidence of OPC effectiveness. These studies assessed the effect of single[8] and multiple[9] doses of OPC or the effect of different timing of co-administration of OPC[10] (i.e. simultaneous versus staggered dosing) with levodopa/DDCI on S-COMT activity and on the PK of levodopa. Collectively, these studies demonstrated that OPC results in a dose- and concentration-dependent inhibition of S-COMT activity that was associated with increased levodopa exposure.

In summary, the clinical development program of OPC assessed pharmacodynamic measures of COMT inhibition, levodopa exposure, and PD motor function. Overall, this data provides cumulative evidence of effectiveness for OPC 50 mg QD dose administered at bedtime.

[8] Study BIA-91067-101.
[9] Study BIA-91067-102.
[10] Study BIA-91067-107; Study BIA-91067-110; Study BIA-91067-117; BIA-91067-114; Study BIA-91067-118; Study BIA-91067-123; Study BIA-91067-124.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general PD patient population. The pivotal Phase 3 studies (BIA-91067-301 and BIA-91067-3012) demonstrated that OPC 50 mg QD administered at bedtime are superior to placebo in reducing OFF-time in PD patients with motor fluctuations (See Section 3.3.1). Additionally, OPC 50 mg administered once daily in patients with PD taking levodopa/DDCI was well tolerated in the 14- to 15-week DB period and in the 1-year open-label extension period. The applicant stated that the incidence of overall treatment emergent adverse events (TEAEs) reported in the Phase 3 studies was similar in the OPC 50 mg (64.2% of subjects) and placebo (57.2%) groups. Incidences of serious TEAEs in the OPC 50 mg and placebo-treated groups (4.9% and 4.3%, respectively) and TEAEs leading to discontinuation (9.1% and 7.4%, respectively) were low and similar between groups (For safety review, please see clinical review).

Studies BIA-91067-301 and BIA-91067-302 assessed 3 doses of opicapone (5 mg[11], 25 mg, and 50 mg) administered once daily at bedtime. The choice of these doses to study in the Phase 3 studies was based on the results from multiple Phase 1 studies in healthy subjects (Studies BIA-91067-102, BIA-91067-105, BIA-91067-118, and BIA-91067-123) and Phase 2 studies in PD patients (Studies BIA-91067-201 and BIA-91067-202). The Phase 1 studies showed that administration of 5 mg to 50 mg OPC QD resulted in dose-related inhibition of S-COMT (up to 99% peak S-COMT inhibition) that translated into OPC dose-related increases in levodopa exposure (for more details, please see Section 3.3.1 and Section 4.4.3). Moreover, the multiple-dose, Phase 2 Study BIA-91067-202 indicated that the dose-dependent effect on S-COMT and levodopa exposure after multiple administration of OPC (5, 15, 30 mg administered once daily in the morning 1 hour prior to levodopa/DDCI for 21 to 28 days) translates into a dose-dependent reduction in the total daily OFF-time (see section 3.3.1).

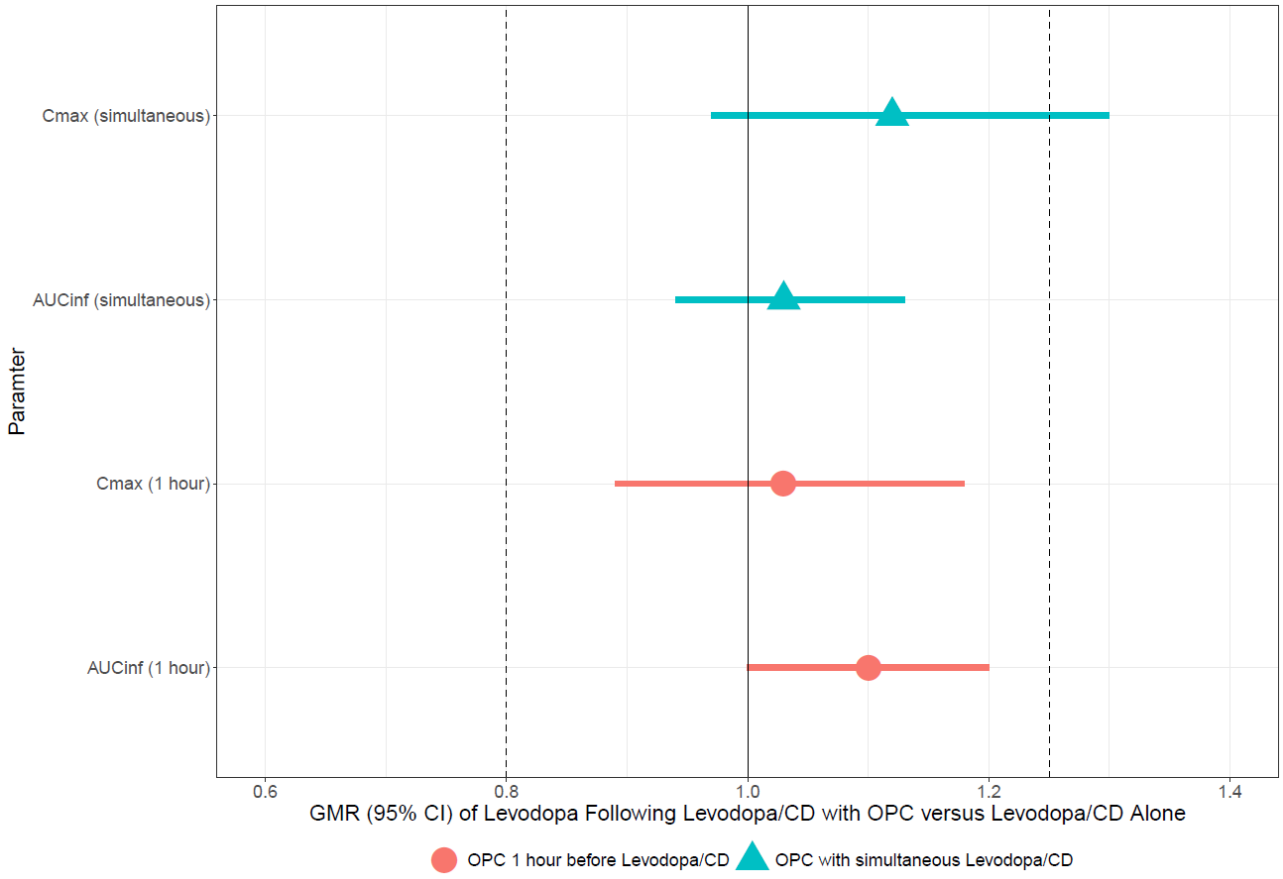
In the Phase 3 studies, the last dose of levodopa/DDCI was administered 1 hour before OPC QD bedtime dosing. The bedtime recommendation was based on the results from the Phase 1 Study BIA-91067-123. Study BIA-91067-123 was conducted to determine the effect of administration of non-micronized OPC (5, 15, or 50 mg) QD at bedtime on levodopa exposure. This study demonstrated a dose-dependent increase in the extent of exposure (as assessed by AUC) to levodopa over the evaluated OPC dose range. The mean 3-OMD C_{max} and AUC_{last} values also decreased in a dose-dependent manner. On Day 11, the peak ($E_{max}I$) and extent ($AUEC_{0-24}$) of S-COMT inhibition was dose-dependently greater for all OPC doses (5, 15, and 50 mg QD) than with placebo. A peak S-COMT inhibition of 99% was observed on Day 11 for the 50 mg OPC dose level, suggesting that there would be little additional benefit of higher OPC doses on maximum S-COMT inhibition.

The recommendation of 1-hour staggered dosing from the levodopa/carbidopa administration was based on observation from Phase 1 studies where OPC was administered either

[11] Assessed only in Study BIA-91067-301.

simultaneously, 1 hour before, at least 10 hours before, or 12 hours before levodopa/DDCI administration. The applicant indicated that in some studies the peak levodopa was attenuated when OPC was administered simultaneously and therefore, recommended administration of levodopa/DDCI 1 hour apart from OPC. However, this observation is not consistent across the Phase 1 studies where levodopa/carbidopa was administered (Refer to section 4.4.3). Additionally, Study BIA-91067-117 evaluated the effect of single-dose OPC and single-dose immediate release (IR) levodopa/carbidopa administered simultaneously or 1 hour apart in a cross-over manner. Results of this study indicated that levodopa peak concentration was similar when administered simultaneously versus 1 hour apart from OPC (Figure 4; Table 14). Therefore, the review team believes 1-hour staggered dosing of levodopa/CD with OPC is not required.

Figure 4: Effect of 1-hour OPC Staggered Dosing versus OPC Simultaneous Administration on Levodopa Exposure Following Levodopa/CD (Study BIA-91067-117)



Source: reviewer analysis

In summary, the review team finds that the clinical pharmacology information presented in this application supports the dosing recommendation for the general population. Therefore, 50 mg QD dosing of OPC at bedtime for the general PD population is acceptable.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, dose optimization is required for subjects with moderate hepatic impairment (Child-Pugh B). Avoid use of ONGENTYS for subjects with severe hepatic (Child-Pugh C) or patients with ESRD (CLcr<15 mL/min). No dose adjustments are needed based on age, body weight, sex or race.

Hepatic Impairment:

The applicant conducted two separate studies to evaluate the effect of mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment on OPC exposure (Studies NBI-OPC-1705 and BIA-91067-106).

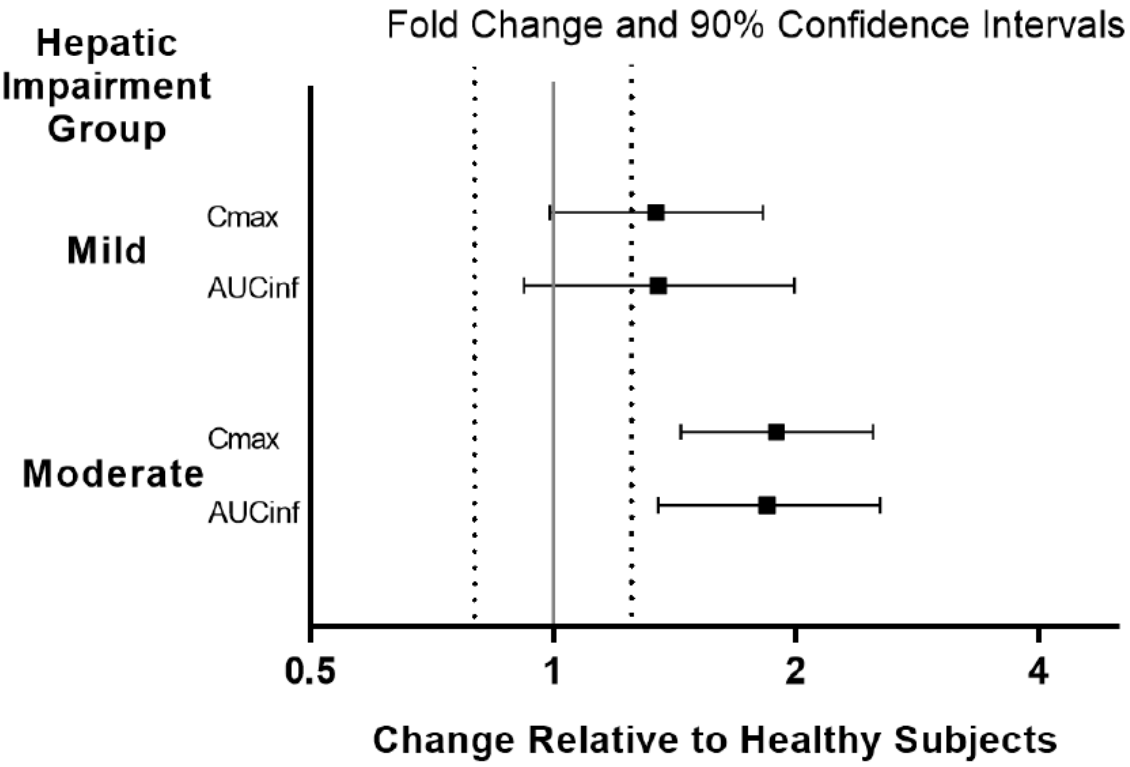
Following a single dose of 50 mg OPC, geometric mean C_{max} and AUC_{inf} parameters for OPC were 34% and 35% higher in subjects with mild hepatic impairment compared with matched subjects with normal hepatic function.

Following a single dose of 50 mg OPC, the geometric mean OPC C_{max} and AUC_{inf} values in subjects with moderate hepatic impairment were 89% and 84% higher than the observed values in matched healthy subjects with normal hepatic function (Figure 5). Plasma protein binding of opicapone was high, with unbound fractions only detected in 3 healthy subjects (range of 0.14 to 0.3 %) and in 5 subjects with moderate hepatic impairment (range of 0.08 to 0.27%). This suggests similar unbound concentrations in subjects with moderate hepatic impairment as compared to normal group.

Based on the modest effect of mild hepatic impairment (Child-Pugh score A) on OPC PK, no dose adjustment is required in these patients. However, based on the approximate doubling of OPC exposure in patients with moderate hepatic impairment, the recommended OPC dose in patients with moderate hepatic impairment (Child-Pugh score B) is 25 mg OPC QD. OPC PK has not been evaluated in patients with severe hepatic impairment; therefore, the use of OPC in these patients should be avoided.

Two-pronged explanation for making such decision is summarized here. First, the population with severe hepatic impairment is not prevalent in the PD patients (as discussed with the medical team leader, Dr. Gerald Podskalny). Second, the lowest available strength of OPC capsule is 25 mg which is recommended for subjects with moderate hepatic impairment. Given that OPC is almost exclusively cleared through hepatic metabolism, it may be reasonable to predict that subjects with severe hepatic impairment may have even higher effect on OPC exposure.

Figure 5: OPC Exposure Changes in Mild and Moderate Hepatic Impairment.



Source: Summary of Clinical Pharmacology, Figure 19. Adapted from Studies BIA-91067-106 Table 13 and NBI-OPC-1705 Table8. Dotted lines indicate 0.80 to 1.25 interval.

Renal Impairment:

The renal route of elimination is a minor excretion pathway for OPC (<1%). A clinical pharmacology study to evaluate the impact of renal impairment on the pharmacokinetics of OPC was not conducted. Instead, a Pop-PK approach (Report 2018-CP-198) was used to assess the impact of renal impairment on the exposure of OPC. Creatinine clearance was not identified as a significant covariate impacting OPC PK in the Pop-PK analysis, and model-simulated exposures for mild and moderate renal impairment were not significantly different from exposures with normal renal function. No OPC dose adjustment is, therefore, recommended in patients with mild or moderate renal impairment.

Patients with severe renal impairment or end stage renal disease (ESRD) (i.e. CLcr<30 mL/min) were not included in any of the studies with OPC. OPC is mainly eliminated through metabolism with the Phase 2 hepatic metabolizing enzymes (mainly SULT). Unlike the Phase 1 metabolizing enzymes, which can be affected by severe renal impairment, there is no sufficient data suggesting that severe renal impairment can affect the metabolic capacity of Phase 2 enzymes. While one may argue that OPC is a highly protein bound drug and severe renal impairment may affect the

unbound fraction, as reported by Benet et al, there may not be any significant clinical relevance to the changes in protein binding [12].

Given that renal impairment is a minor route of elimination (<1% of opicapone is eliminated unchanged and the total radioactivity observed in urine for all opicapone related material is 5%), and no changes in exposures as a result of mild and moderate renal impairment, the review team recommends no dose adjustment in severe renal impairment. However, discontinue opicapone if any tolerability issues arise. No dosing recommendations, however, can be made for patients with ESRD (CLcr<15 mL/min). Therefore, ONGENTYS should be avoided in ESRD special population.

Race:

BIA-91067-126 was a Phase 1, randomized, double-blind, parallel-group, placebo-controlled, multiple-ascending dose study that assessed the potential effect of Japanese ethnicity on the PK of OPC and its metabolites. The study population consisted of 105 healthy male and female subjects (51 Caucasian and 54 Japanese). The study comprised 3 treatment groups. In each group, up to 10 subjects were administered placebo orally and up to 27 subjects were administered OPC (5, 25, or 50 mg) orally QD following an overnight fast of at least 8 hours for 10 days. The geometric mean ratios for C_{max} and AUC_{inf} following the first dose of 50 mg OPC were ~15% and 26% higher in healthy Japanese subjects compared to matched healthy Caucasians. Following 10 days of OPC 50 mg QD dosing, the geometric mean ratios for C_{max} and AUC_{last} were ~20% and 19% higher in healthy Japanese subjects compared to matched healthy Caucasians.

In addition, Pop-PK analysis (Report 2018-CP-198) predicted an approximate 40% higher peak and overall exposure in Asian subjects but did not identify a change in opicapone pharmacokinetics in Black subjects. No dose adjustment is necessary based on race.

Age:

Study BIA-91067-105 evaluated the effect of age on the PK of OPC. The study population consisted of 24 healthy male subjects (12 young [aged 18 to 40 years, inclusive] and 12 elderly [aged ≥65 years]). Each subject was administered 30 mg QD OPC orally for 7 days after an overnight fast of at least 8 hours. Following both single and multiple doses of OPC, OPC PK was generally comparable between young and elderly subjects. The geometric mean ratios for OPC C_{max} and AUC_{last} following single and multiple doses of OPC were 9% to 28% higher in elderly subjects compared to young subjects.

Sex and Weight:

[12] Benet, Leslie Z., and Betty-Ann Hoener. "Changes in plasma protein binding have little clinical relevance." Clinical Pharmacology & Therapeutics 71.3 (2002): 115-121.

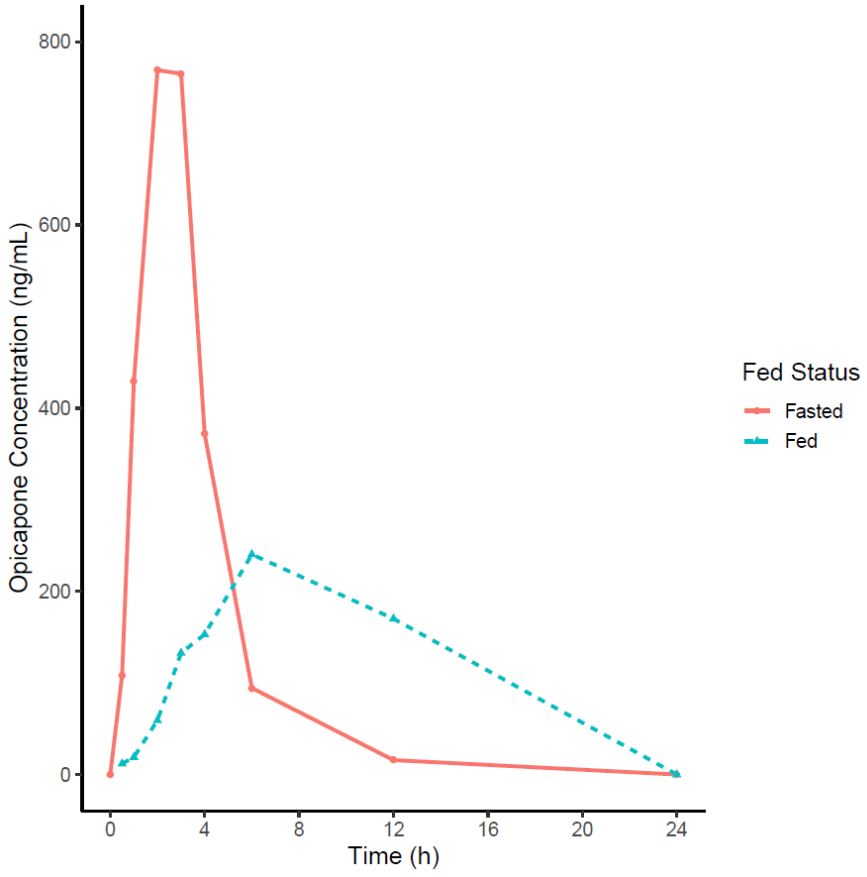
Evaluation of the effect of these intrinsic factors was conducted as part of the Pop-PK analysis (Report 2018-CP-198). Population PK analysis concluded that weight, and sex are not expected to significantly affect the exposure of OPC (refer to Section 4.2 for more details).

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food effect:

The effect of a moderate-fat/calorie meal on OPC PK was investigated after multiple doses of OPC 50 mg (micronized formulation) QD in Study BIA-91067-128. OPC C_{max} and AUC_{last} values were decreased by 62% and 31%, respectively, following administration under fed relative to fasted conditions. The mean plasma OPC concentration - time profiles in the fasted and fed state are shown below (Figure 6).

Figure 6: Mean plasma concentration (ng/mL)-time (hours) profiles of OPC in the fasted state (red line) and fed state (blue line).



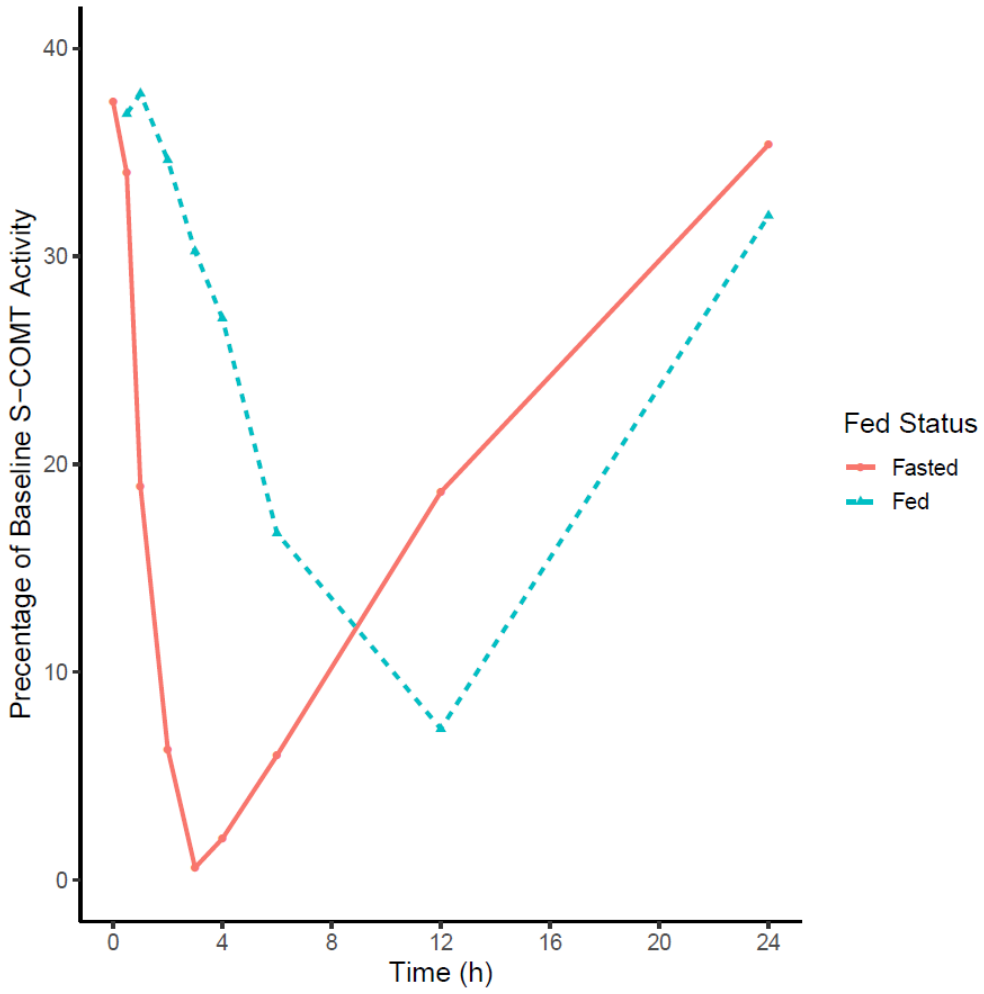
Source: figure re-created by the reviewer using data from Study BIA-91067-128

Mean S-COMT activity time profile, as a percentage of change in relation to baseline, in the fed and fasted condition is presented in Figure 7. Following 9 days (D9, fasted state) of a 12-day QD administration of 50 mg OPC, maximum S-COMT inhibition [E_{max} (%)] was 99%. S-COMT maximum inhibition (tE_{max}) was attained at 2.3 hours post-dose. On D10, following a moderate fat meal (fed state), E_{max} (%) was 96% and the tE_{max} increased to 11.6 hours post-dose. It is noted that the mean $AUEC_{0-24}$ (pmol/mg Hb/h.h) was similar between both fast and fed states although 4% higher in fed state.

The effect of high fat meal was not evaluated for the micronized formulation[13]. In Phase 3 study BIA-91067-301, OPC was administered without regard to food. Whereas in the second Phase 3 study, BIA-91067-302, the protocol specified that subjects should fast for at least 1 hour before and 1 hour after the intake of OPC. The effect of food on S-COMT activity at 8-24 hours (supposedly the time of the next day levodopa/carbidopa dose after bedtime dosing of OPC) is similar but somewhat higher under fed condition in healthy subjects. However, given the effect of high-fat meal on OPC exposure is unknown and may result in further reduction in exposure of OPC and may further delay of the tE_{max}, OPC should be administered 1 hour away from food; as done in Study BIA-91067-302.

[13] Study BIA-91067-104 evaluated the effect of high-fat meal following single dose administration of 50 mg dose of the nonmicronized OPC formulation. Therefore, the effect of high-fat meal on micronized formulation is not known.

Figure 7: Mean S-COMT activity-time profiles, as a percentage of change in relation to baseline (D1 pre-dose), following repeated doses of 50 mg OPC administered in fasted (red line) or fed state (blue line) in healthy subjects.



Source: Figure re-created by the reviewer using data from Study BIA-91067-128

Drug-Drug Interactions:

In vitro studies for major CYP enzymes and transporters:

As a substrate:

Metabolism of OPC in human liver microsomes was negligible, indicating that inhibition or induction of CYP enzymes by co-administered drugs is unlikely to result in clinically significant changes in OPC exposures. Sulfation, through SULT1A1, appears to be the major metabolic pathway (generating BIA 9-1103). Other metabolic pathways involved in BIA 9-1067 are reduction (generating BIA 9-1079) and methylation (generating BIA 9-1100) and glucuronidation (generating BIA 9-1106).

In vitro studies indicated that OPC is a substrate of uptake transporters: OATP1B3 (Study report Tebu-02-30Jun2014) and OATP2B1 (Study report SRAL120824). OPC also appeared to be a substrate for efflux transporters: BCRP, and MRP2 (Study reports: SRAL120824 and SRAL121106). OPC may be also a substrate for efflux transporter P-gp (MDR1) (as per Study reports: SRAL140627), although the results were not consistent across all in vitro studies (Study reports SRAL121106 and SRAL120824).

Consistent with the FDA guidance for drug interaction, OPC was not evaluated as a substrate for kidney proximal tubule cell uptake (OAT1, OAT3, and OCT2) or efflux (MATE1 and MATE2-K) transporters, as the contribution of renal clearance to the elimination of OPC was shown to be minimal (Study BIA-91067-130).

As a perpetrator:

In human hepatic microsomes, OPC and BIA 9-1103 caused <30% inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6, and CYP2E1 activities at the highest concentrations tested (10 µg/mL OPC and 30 µg/mL BIA 9-1103). Both compounds inhibited CYP2C8 and CYP2C9, with Ki values of 0.9 and 18 µg/mL for OPC and IC50 values of 6.7 and 20.7 µg/mL for BIA 9-1103, respectively. Time-dependent inhibition was not observed for either OPC or BIA 9-1103 with any of the CYP isoforms evaluated. It is noted that the free (unbound) C_{max} values for both OPC and BIA 9-1103 in human plasma at the therapeutic dose of 50 mg are estimated to be approximately 0.005 µg/mL[14]. Therefore, clinically relevant drug interactions mediated through CYP enzyme inhibition perpetrated by OPC or its metabolite BIA 9-1103 are considered unlikely when therapeutic exposure and plasma protein binding are taken into account.

[14] According to Study NBI-OPC-1706 and using the default minimum plasma free fraction of 0.01 promulgated in the FDA Draft Guidance for Industry on In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interactions.

OPC and BIA 9-1103 were not observed to be inducers of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes. Likewise, OPC and BIA 9-1103 did not induce CYP1A2, CYP2B6, and CYP3A4 activities, or gene expression of these enzymes in human hepatocellular carcinoma cells (HepaRG).

OPC and BIA 9-1103 inhibited OAT1, OAT3, OATP1B1, and OATP1B3, with IC50 values of 9.2, 4.4, 0.5, and 1.4 µg/mL for OPC, and 13.2, 2.6, 2.8[15], and 7.5 µg/mL for BIA 9-1103, respectively. OPC and BIA 9-1103 did not inhibit MDR1 or BCRP, OCT1, OCT2, and MATE1. OPC demonstrated marginal inhibition (52% at the highest tested concentration: 30 µg/mL) of MATE2-K, while BIA 9-1103 did not inhibit MATE2-K. Based on these findings there appears to be a potential for clinically relevant inhibition of OATP1B1/3 by OPC[16].

In vivo clinical studies:

The applicant conducted clinical DDI studies to evaluate the clinical relevance of the in vitro findings. Clinical studies were conducted to evaluate the effect of a potent MDR1 inhibitor, quinidine, on the exposure of OPC following oral administration. The applicant did not conduct any clinical drug interaction studies with BCRP or OATP1B3 inhibitors[17,18,19] Considering the ADME characteristics of OPC and the results of the in vitro studies, the review team agrees with the applicant and do not think that further in vivo evaluation is necessary.[20] Specifically, in vitro studies have shown that OPC has high membrane permeability[21]. Furthermore, in the in vitro studies, OPC is less sensitive a substrate of BCRP than reference compounds; the magnitude of clinical effect of sensitive BCRP compounds is typically low to moderate (2- to 3-fold increase in exposure). The review team note that based on the results of the confirmatory ADME study (Study BIA-91067-130), it can be assumed that 80% of the dose is absorbed (20% excreted unchanged in feces). As such BCRP may play only a limited role in increasing OPC bioavailability if it is completely inhibited. Likewise, in vitro studies demonstrate that OPC is a weak substrate of OATP1B3. The review team note that the tissue: blood ratios following single oral administration of [14C] BIA 9-

[15] Note that the applicant did not submit any data regarding the plasma: blood ratio for BIA 9-1103. However, the reviewer assumed to be same as OPC. This information is not considered critical at this stage as the applicant conducted clinical DDI study with OATP1B1 sensitive substrate. Negative findings of this study preclude the need for further investigation of OATP1B3.

[16] The fraction absorbed and the intestinal availability was considered to equal 1, the ka was set at 0.1/min, the hepatic blood flow was set as 600 mL/min, the blood to plasma concentration ratio was set to 0.5 (as per ZNA15658-004 study report).

[17] Note that OPC is also a substrate for the efflux transporter MRP2 and intestinal uptake transporter OATP2B1. However, we are not aware of a specific inhibitor for these transporters and therefore we are not recommending any labeling language at this point

[18] Examples of BCRP inhibitors are curcumin, cyclosporine A, eltrombopag

[19] Examples of OATP1B3 are atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin, simeprevir

[20] As stated by the applicant in the Response to FDA Information Request submitted on 02/11/2020

[21] In the definitive Caco-2 study, the apparent permeability coefficient (P_{app}) of 100 µM OPC was 3.5×10^{-6} cm/s in the apical-basolateral (AP-BL) direction and 22.7×10^{-6} cm/s in the BL-AP direction (SLV-22092017). The high BL-AP P_{app} indicates that OPC is highly membrane permeable and the limited permeability in the AP-BL direction can be explained by the fact that OPC is a substrate for efflux transporters as indicated previously.

1067 to male albino rats at a target dose level of 10 mg/kg was not significantly different between kidney and liver[22]. Although the sponsor did not evaluate OPC as a substrate for renal transporters, the renal excretion does not play a significant role in OPC elimination. Therefore, it can be concluded that the similar accumulation of OPC in liver and kidney is mainly due to the high membrane permeability of OPC in the highly perfused tissues and not due to the uptake transporter OATP1B3. Taken collectively, we believe the potential for a clinically-relevant increase in OPC exposure through inhibition of OATP1B3 uptake transporter is low.

As mentioned above, the in vitro data did not suggest any clinically relevant drug interaction potential by OPC or its major inactive metabolite, BIA 9-1103 for major CYPs. However, the applicant conducted clinical studies to evaluate the inhibition potential of OPC and its major inactive metabolite, BIA 9-1103, on CYP2C8 (using repaglinide as index substrate), and CYP2C9 (using S-Warfarin as index substrate). However, in vitro studies suggested a potential inhibition of OATP1B1/3 by OPC. The applicant conducted clinical drug interaction study with an index OATP1B1 substrate (using repaglinide). The sponsor's rationale for these studies was to evaluate the relevance of the in vitro findings by carrying out an in vivo study with a sensitive index substrate of the CYP(s) and transporter(s) with the largest R or the largest predicted AUC ratio value for the victim drug[23]. If these in vivo studies show no interactions, in vivo evaluations of other CYPs and transporters with lower potencies (e.g., smaller predicted AUC ratios or larger IC50 or Ki) are not needed. This approach is consistent with the current FDA guidance[24].

As a victim:

Quinidine (as P-gp inhibitor):

Study NBI-OPC-1707 assessed the effect of a single-dose quinidine 600 mg on a single-dose OPC 50 mg administered 1 hour after quinidine administration in healthy subjects (N=20). Quinidine and OPC were administered following an overnight fast of at least 10 hours, and the fasting state continued for 4 hours after OPC dose. Following administration of OPC 1 hour after 600 mg quinidine, median T_{max} for OPC was approximately 1.5 hours later compared to when OPC was administered alone. OPC exposure (C_{max} and AUC parameters) were approximately 30% to 37% lower when administered after quinidine compared to administration alone.

The finding of this study is unexpected. One possible explanation could be an involvement of other intestinal uptake transporters that could have been inhibited by quinidine administration. For example, some in vitro studies showed that quinidine appears to inhibit OATP2B1[25], an intestinal

[22] Based on relative tissue distribution in rat whole body radiograph study (zna15658-003)
[23] Calculated based on the current FDA guidance for in vitro drug interaction
[24] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-metabolism-and-transporter-mediated-drug-drug-interaction-studies-guidance-industry.
[25] Bi YA. (2019). Quantitative Contribution of Six Major Transporters to the Hepatic Uptake of Drugs: "SLC-Phenotyping" Using Primary Human Hepatocytes. J Pharmacol Exp Ther, 370, 72-83.

apical uptake transporter. Indeed, in vitro data (SRAL120824) indicated that OATP2B1 may be involved in OPC absorption[26].

Acetaminophen (for glucuronidation and sulfation)**:**

The applicant conducted Study BIA-91067-125 to investigate the effect of glucuronosyl- and sulfo-transferases inhibition on OPC. The applicant indicated that since acetaminophen is metabolized by glucuronidation and sulfation, high dose of acetaminophen (i.e. 3 g) can result in inhibition of these enzymes. In this study, healthy volunteers (N=28) received either a single dose of 50 mg OPC alone or 1.5 hours after the 3rd dose of 1 g acetaminophen (acetaminophen 1 g doses were administered 6 hours apart).

Following administration of OPC alone or after 3 doses of acetaminophen 1 g there was no relevant difference in median T_{max} of OPC, BIA 9-1103 (OPC sulfate) metabolite, or BIA 9-1106 (glucuronide of OPC) metabolite. The geometric mean ratios (90% confidence interval) for C_{max} and AUC_{inf} of OPC following acetaminophen administration relative to OPC alone were 112.57 (101-125) % and 115 (108-123) %, respectively. The geometric mean ratios (90% confidence interval) for C_{max} and AUC_{inf} of BIA 9-1103 following acetaminophen administration relative to OPC alone were 88 (82-94) % and 89 (83-95) %, respectively. BIA 9-1106 C_{max} and AUC_{last} values were 68% and 83% higher, respectively, following administration of OPC after acetaminophen relative to OPC alone. Nonetheless, the absence of significant changes in OPC concentration following administration with acetaminophen and the decrease in sulphate metabolite and the increase in the glucuronide metabolite indicates that the glucuronidation played a compensatory role to the affected (decrease) exposure to BIA 9-1103. No dosing adjustment in necessary for OPC when administered with acetaminophen.

It is noted that neither the FDA guidance for drug interaction[27] nor the FDA website for drug interaction[28], specify any inhibitor for the Phase 2 glucuronosyl- and sulfo-transferases metabolizing enzymes. Moreover, the University of Washington Drug Interaction Database[29] does not list any potential for interaction of acetaminophen as a perpetrator.

Rasagiline (as selective MAO-B inhibitor)**:**

Study BIA-91067-113 assessed the effect of 1 mg rasagiline (Azilect®; selective MAO-B inhibitor) on the PK of OPC. Healthy volunteers (N=25) received single doses of 50 mg OPC, 50 mg OPC co-administered with 1 mg rasagiline, or 50 mg OPC administered 1 hour before 1 mg rasagiline in a randomized, 3-way crossover manner. The PK parameters of OPC were similar when administered

[26] The inhibitory effect of uptake on OPC was evaluated in terms of the concentration dependent increase of estrone-3-sulfate (an OATP-B substrate). The inhibitory effect on OPC uptake was dependent on the estrone-3-sulfate concentration.
[27] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-study-design-data-analysis-and-clinical-implications-guidance
[28] https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions
[29] https://didb.druginteractionsolutions.org/drug/monograph/69/#ddi-summary

as a single dose concomitantly with, or 1 hour after, OPC compared to administration alone (Table 1).

Levodopa/Carbidopa

Study BIA-91067-117 was a Phase 1, open-label, randomized, gender-balanced, crossover study to investigate the PK of levodopa following a single oral dose of OPC (non-micronized) administered simultaneously with IR 100/25 mg levodopa/carbidopa (Sinemet® 100/25 tablets) when compared with a single oral dose of OPC administered 1 hour before IR 100/25 mg levodopa/carbidopa. The study population consisted of 18 healthy male and female subjects. In 4 consecutive treatment periods, subjects received, in random sequence: a single 50 mg dose of OPC co-administered simultaneously with a single dose of 100/25 mg levodopa/carbidopa; a single 50 mg dose of OPC administered 1 hour before a single dose of 100/25 mg levodopa/carbidopa; a single 50 mg dose of OPC administered alone; a single dose of 100/25 mg levodopa/carbidopa administered alone. Treatment periods were separated by washout periods of at least 21 days. Both OPC and levodopa/carbidopa were administered following an overnight fast of at least 8 hours. Blood samples for PK and pharmacodynamic assays were collected at intervals up to 72 hours post-dose (relative to OPC for PK, and relative to levodopa/carbidopa for pharmacodynamics where applicable). Following simultaneous coadministration with levodopa/carbidopa, OPC C_{max} and AUC_{inf} parameters were generally similar in all treatment groups. The geometric mean ratio for OPC 50 mg when administered simultaneously with levodopa/carbidopa relative to OPC 50 mg alone (90% confidence interval) for C_{max} and AUC_{inf} were 100 (84-118) and 104 (87-125), respectively. The geometric mean ratio for OPC 50 mg when administered 1 hour before levodopa/carbidopa relative to OPC 50 mg alone (90% confidence interval) for C_{max} and AUC_{inf} were 91 (77-107) and 105 (88-125), respectively.

Table 1 Clinical Drug Interaction Study Results for Opicapone as a Victim.

Perpetrator Drug	**OPC PK Parameter**	**GMR (%)**	**90 % CI (%)**
OPC (50 mg) administered 1.5 hour after 3 doses of 1 g Acetaminophen	C_{max}	113	101- 125
	AUC_{inf}	115	108- 123
OPC (50 mg) with single-dose Quinidine 600 mg administered 1 hour before OPC	C_{max}	70	60-82
	AUC_{inf}	69	55-86
OPC (50 mg) with single-dose rasagiline 1 mg administered concomitantly with 50 mg OPC	C_{max}	100	88. – 114
	AUC_{inf}	105	92 – 120
OPC (50 mg) with single-dose rasagiline 1 mg	C_{max}	112	98- 127
	AUC_{inf}	107	94 – 123

administered 1 hour after 50 mg OPC			
OPC (50 mg) with single dose levodopa/carbidopa (Sinemet® 100/25 tablets) administered simultaneously	C_{max}	100	84-118
	AUC_{inf}	104	87-125
OPC (50 mg) with single dose levodopa/carbidopa (Sinemet® 100/25 tablets) administered 1 hour after 50 mg OPC	C_{max}	91	77-107
	AUC_{inf}	105	88-125

As a perpetrator:

CYP2C9 inhibition:

Study BIA-91067-127 assessed the effect of repeated dose of OPC (micronized formulation) on the PK of CYP2C9 substrate S-Warfarin. Healthy volunteers (N=20) received single dose of 25 mg warfarin (5×5 mg Varfine® tablets) alone or co-administered with 50 mg OPC following 8 days of OPC administration (475 mg loading dose on Days 1 and 2 and 50 mg doses from Days 3 to 8) in a 2-way crossover manner. S-warfarin C_{max} were comparable when warfarin was co-administered with OPC compared to warfarin alone (the 90% CIs of the geometric mean ratios were within the 80% to 125% interval). S-warfarin AUC_{inf} were slightly decreased (12%) when warfarin was co-administered with OPC. In addition, the applicant also assessed the effect of OPC on R-warfarin as well as INR. There were no significant changes in the R-warfarin, nor in the INR following administration with OPC. The INR_{max}, and AUCINR values were comparable when warfarin was co-administered with OPC relative to when warfarin was administered alone; the 90% confidence intervals were within the 80% to 125% interval.

CYP2C8 and OATP1B1 inhibition:

BIA-91067-115 assessed the effect of single dose OPC 25 mg (non-micronized)[30] on a single-dose repaglinide (0.5 mg). Healthy volunteers (N=27) received single dose of 0.5 mg repaglinide alone or a single dose of 0.5 mg repaglinide administered 1.25 hours after a single dose of 25 mg OPC in a 2-way crossover manner. Repaglinide and OPC were administered following an overnight fast of at least 8 hours, and the fasting state continued until 15 minutes after repaglinide was administered, at which point a standard breakfast was administered. Repaglinide C_{max}, and AUC_{inf} increased by 31% and 9%, respectively, in presence of OPC 25 mg.

[30] Using nonmicronized formulation which provides approximately half of the exposure of the micronized formulation

To assess the effect of both OPC and its sulphate metabolite at steady state on repaglinide PK at the therapeutic dose of OPC (i.e. 50 mg[31]), the applicant conducted Study NBI-OPC-1708. In this study, healthy volunteers (N=18) received a single dose of 0.5 mg repaglinide on Days 1 and 15, and OPC 50 mg qd on Days 2 through 15. Repaglinide and OPC were administered following an overnight fast of at least 8 hours, and the fasting state continued until 2 hours post-dose. Following OPC 50 mg administered once daily for 14 consecutive days, the geometric mean ratios of repaglinide following single dose (0.5 mg) for C_{max} and AUC ranged from 93% to 100% and the 90% confidence intervals were fully contained within the limits of 80-125%.

It is worth noting that when considering the effect of OPC as a perpetrator, the sponsor should use 50 mg of OPC micronized formulation as this is considered the dose that should maximize the possibility of identifying a DDI. However, larger interaction was seen when OPC 25 mg was used in Study BIA-91067-115. The reasons for this discrepancy between the 2 studies are not clear. There are few differences between both studies. For example, BIA-91067-115 studied the effect of a single dose of 25 mg OPC using non-micronized formulation which provides exposure similar to 12.5 mg of OPC using the micronized formulation. Study NBI-OPC-1708 on the other hand studied the effect of multiple dose of 50 mg OPC using the micronized formulation. Moreover, the timing of repaglinide administration (staggered administration by 1.25 h versus co-administration with OPC) was different between both studies. Another difference was that in BIA-91067-115, standard breakfast was administered 15 minutes after repaglinide administration, whereas in NBI-OPC-1708 a standard breakfast was administered 2 hours following drug administration. However, none of these differences appear to result in such observed differences. While repaglinide is also a substrate for CYP3A4, in vitro studies did not appear to indicate any potential for CYP3A4 induction by OPC or its major metabolite BIA 9-1103. Additionally, one may expect that staggered administration would have potentially led to lower effect on the repaglinide C_{max}, which is not the case. Furthermore, it is not clear if the differences in the timing of food administration following repaglinide administration (i.e. 15 min in BIA-91067-115 versus 2 h in NBI-OPC-1708) could result in such difference. Although it has been reported that food decreases the C_{max} of repaglinide by 20% and the AUC by 12%, the timing of food administration was standardized in both periods (i.e. with or without OPC) for both studies. Differences in OPC exposures as a result of dose or food effect between both studies doesn't seem to provide logical explanation for such discrepancy.

Nonetheless, it is reasonable to conclude that there is low potential for OPC drug interaction with major transporters. As there was no clinical drug interaction observed with repaglinide (a sensitive OATP1B1 substrate) with OPC 50 mg (micronized) when administered concomitantly, there is a low potential for OPC drug interactions with other transporters that had higher IC50 or smaller predicted AUC ratio values.

[31] Using micronized formulation which is bioequivalent to the to-be-marketed formulation

Table 2 Clinical Drug Interaction Study Results for Opicapone as a Perpetrator.

Victim Drug	PK Parameter of victim drug	GMR (%)	90 % CI
Warfarin (25 mg) with single-dose 25 mg OPC[32]	S-Warfarin C_{max}	103	96-110
	S-Warfarin AUC_{inf}	104	98-110
	R-Warfarin C_{max}	105	99-111
	R-Warfarin AUC_{inf}	104	97-111
Warfarin (25 mg) with multiple-dose OPC (50 mg)[33]	S-Warfarin C_{max}	101	84-120
	S-Warfarin AUC_{inf}	88	80-97
	R-Warfarin C_{max}	98	82-116
	R-Warfarin AUC_{inf}	87	79-97
Repaglinide (0.5 mg) with single-dose 25 mg OPC[34]	C_{max}	131	114- 151
	AUC_{inf}	109	102-117
Repaglinide (0.5 mg) with multiple-dose 50 mg OPC	C_{max}	93	82-105
	AUC_{last}	97	90-105
Rasagiline (1 mg) administered concomitantly with single-dose 50 mg OPC[35]	C_{max}	101	87-117
	AUC_{inf}	10	96-109
Rasagiline (1 mg) administered 1 hour after single-dose 50 mg OPC[36]	C_{max}	100	86-116
	AUC_{inf}	102	96-109

Source: Tables generated by FDA reviewer from data sets with DDI individual study reports.

[32] Study was done with the nonmicronized formulation which provides approximately half of the exposure of the micronized formulation.
[33] Loading dose of 475 mg qd of OPC for the first 2 days, followed by 50 mg qd on Day 3-Day 7.
[34] Study was done with the nonmicronized formulation which provides approximately half of the exposure of the micronized formulation
[35] Study was done with the nonmicronized formulation which provides approximately half of the exposure of the micronized formulation
[36] Study was done with the nonmicronized formulation which provides approximately half of the exposure of the micronized formulation

Other PK Drug Interaction Studies:

Levodopa

The primary mechanism of action of OPC is to inhibit peripheral COMT, which when OPC and levodopa/carbidopa are co-administered, results in increased peak and overall exposure to levodopa and decreased exposure to 3-OMD. The applicant conducted several clinical studies in both healthy subjects as well PD patients to demonstrate the effect of OPC administration on levodopa exposure following co-administration of OPC with levodopa/carbidopa either simultaneously or as staggered dosing (up to 12 hours staggered dosing). These studies were conducted either during the development to allow for dose selection for the pivotal Phase 3 studies (Studies BIA-91067-108, BIA-91067-110, BIA-91067-117, BIA-91067-114, BIA-91067-118, BIA-91067-123, BIA-91067-124, BIA-91067-201, BIA-91067-202)[37] or after the completion of the Phase 3 studies to provide accurate labeling language (Study NBI-OPC-1706). Overall, these studies indicated that OPC inhibited S-COMT activity, increased levodopa exposure, and decreased 3-OMD exposure compared to administration of levodopa/DDCI alone in a dose dependent manner. Moreover, these studies showed that administration of OPC with levodopa/carbidopa either simultaneously or with staggered administration results in an increase in overall levodopa exposure (See Section 4.4.3). As such, no restriction is required on the coadministration of OPC and levodopa/carbidopa.

Study NBI-OPC-1706 was conducted after Phase 3 studies. The study assessed the effect of single and repeated doses (14 days of once-daily dosing) of OPC 50 mg on levodopa PK in subjects with PD. Following 50 mg qd micronized OPC at bedtime, an increase in peak and overall exposure to levodopa and corresponding decrease in exposure to 3-OMD was observed for each levodopa dose (administered as levodopa/carbidopa 100/25 every 3 hours [q3h] and every 4 hours [q4h]) compared to baseline. For both q3h and q4h levodopa dosing, OPC 50 mg administered qd for 14 days was associated with an increase in overall levodopa C_{max} (43 to 44% higher; Figure 3) and AUC_{last} (62 to 94% higher; Figure 3).

Carbidopa

The effect of OPC 50 mg (micronized) on carbidopa was evaluated in Study BIA-91067-124[38]. Study BIA-91067-124 was a Phase 1, double-blind, randomized, gender-balanced, placebo-controlled

[37] The applicant also evaluated the effect of concomitant administration of OPC with LD/benserazide in Studies: BIA-91067-107 and BIA-91067-109. Moreover, in studies BIA-91067-118, BIA-91067-123, BIA-91067-201, BIA-91067-202, subjects received either LD/carbidopa or LD/benserazide. However, because benserazide is not approved in US, these studies were not part of the review.

[38] While the applicant assessed the effect of OPC administration on carbidopa exposure as part of other studies in healthy volunteers and PD patients, results of this studies are only considered supportive because these studies used the nonmicronized formulation. Nonetheless, all of these studies indicated that when OPC and LD/carbidopa are administered either simultaneously or up to 10 hours apart, peak and overall exposure to carbidopa was comparable to when LD/carbidopa was administered alone.

study in healthy volunteers (N=80). The study investigated the effect of steady-state OPC (25, 50, and 75 mg; N=16 per dose level) versus placebo (N=16) and 200 mg entacapone (N=16) on the PK of IR 100/25 mg levodopa/carbidopa (Sinemet® 100/25 tablets) tid (5 hours apart). OPC or placebo was administered once daily on Days 1 to 11 in the evening after a 2 hour fast. Levodopa/carbidopa was administered on Day 12 approximately 10 hours after OPC evening dosing following an overnight fast of at least 8 hours, and subjects remained fasted until approximately 2 hours after the levodopa dose. The C_{max} and AUC parameters of carbidopa after all doses of OPC (and entacapone) were generally comparable to those after placebo administration following all administrations of levodopa/carbidopa. Following OPC 50 mg (micronized) qd for 11 days, the geometric mean ratios of carbidopa (90% confidence interval) of C_{max} and AUC_{5h} (relative to placebo) were 96 (70-131) and 99 (76-128)[39], respectively, following administration of third 100/25 mg levodopa/carbidopa dose with OPC versus third 100/25 mg levodopa/carbidopa dose plus placebo on Day 12.

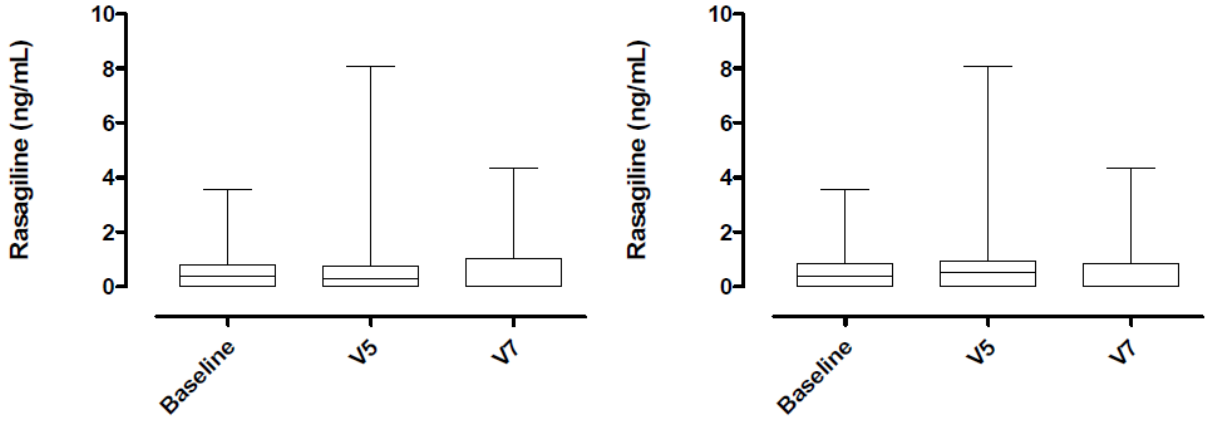
Rasagiline

Study BIA-91067-112 assessed the effect of OPC (non-micronized) on the PK of the selective MAO-B inhibitor rasagiline (1 mg standard-release Azilect®). Healthy volunteers (N=24) received single doses of rasagiline, rasagiline co-administered with 50 mg OPC, or rasagiline administered 1 hour after 50 mg OPC in a randomized, 3-way crossover manner. The PK parameters of rasagiline were similar when administered as a single dose concomitantly with, or 1 hour after, OPC compared to administration alone; 90% CIs for C_{max} and AUC parameters were within 80% to 125% (Table 2).

Moreover, in a pooled analysis (Report BIA-91067-AntiPD001) of subjects with PD from the Phase 3 studies (BIA-91067-301 and BIA-91067-302), rasagiline concentrations were assessed at baseline (ie, randomization; N=66 subjects), Visit 5 (up to 49 days after baseline; N=56 subjects), and Visit 7 (up to 95 days after baseline; N=48 subjects) for subjects receiving 25 or 50 mg qd OPC (combined analysis) and subjects receiving only 50 mg qd OPC (N=43, 37, and 32 for randomization, Visit 5, and Visit 7, respectively). There were no apparent relevant differences in mean pooled plasma concentrations of rasagiline when comparing Visits 5 and 7 with baseline in the combined 25/50 mg OPC group or the 50 mg OPC group. Thus, the PK of rasagiline was unaffected by OPC in studies with healthy or PD subjects (Figure 8).

[39] Note that the study is parallel-group which may explain the width of the 90% confidence interval.

Figure 8: Mean Pooled Plasma Rasagiline Concentrations per Visit for the 25 and 50 mg OPC Dose Levels Combined (Left) and the 50 mg OPC Dose Level Alone (Right) (Report BIA-91067-AntiPD001)



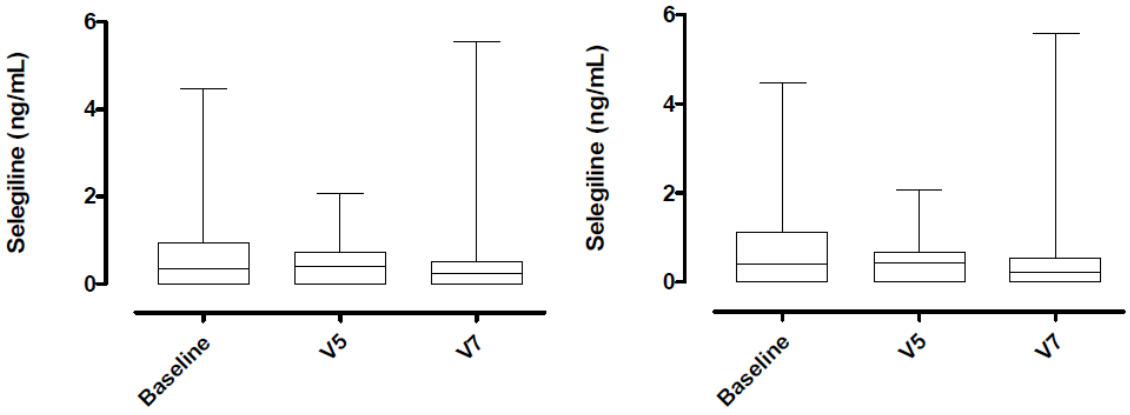
Source: Report BIA-91067-AntiPD001 Figure 9 and Figure 10. V = visit.

Other anti-PD medications

Selegiline

In a pooled analysis of subjects with PD from the Phase 3 studies, (BIA-91067-301 and BIA-91067-302), selegiline concentrations were assessed at baseline (ie, randomization; N=43 subjects), Visit 5 (up to 49 days after baseline; N=41 subjects), and Visit 7 (up to 95 days after baseline; N=35 subjects) for subjects receiving 25 or 50 mg qd OPC (combined analysis) and subjects receiving only 50 mg qd OPC (N=19, 19, and 14 for randomization, Visit 5, and Visit 7, respectively). There were no apparent relevant differences in mean pooled plasma concentrations of selegiline when comparing Visits 5 and 7 with baseline in the combined 25/50 mg OPC group or the 50 mg OPC group. Based on these data, selegiline exposure is not affected when co-administered with OPC (Figure 9).

Figure 9: Mean Pooled Plasma Selegiline Concentrations per Visit for the 25 and 50 mg OPC Dose Levels Combined (Left) and the 50 mg OPC Dose Level Alone (Right) (Report BIA-91067-AntiPD001)

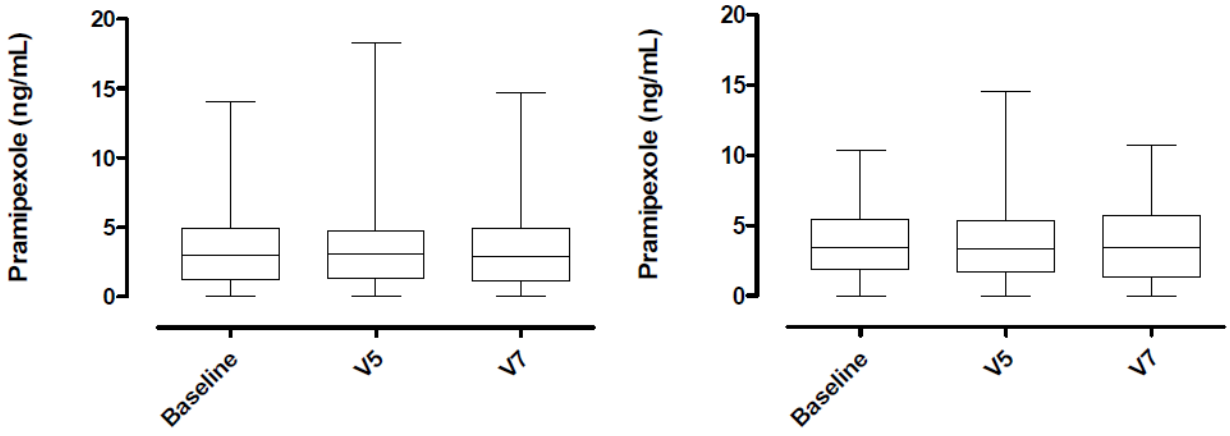


Source: Report BIA-91067-AntiPD001 Figure 5 and Figure 6. V = visit.

Pramipexole

In a pooled analysis of subjects with PD from the Phase 3 studies, (BIA-91067-301 and BIA-91067-302), pramipexole concentrations were assessed at baseline (ie, randomization; N=181 subjects), Visit 5 (up to 49 days after baseline; N=163 subjects), and Visit 7 (up to 95 days after baseline; N=156 subjects) for subjects receiving 25 or 50 mg qd OPC (combined analysis) and subjects receiving only 50 mg qd OPC (N=93, 81, and 80 for randomization, Visit 5, and Visit 7, respectively). There were no relevant differences in mean pooled plasma concentrations of pramipexole when comparing Visits 5 and 7 with baseline in the combined 25/50 mg OPC group or the 50 mg OPC group (Figure 10).

Figure 10: Mean Pooled Plasma Pramipexole Concentrations per Visit for the 25 and 50 mg OPC Dose Levels Combined (Left) and the 50 mg OPC Dose Level Alone (Right) (Report BIA-91067-AntiPD001)

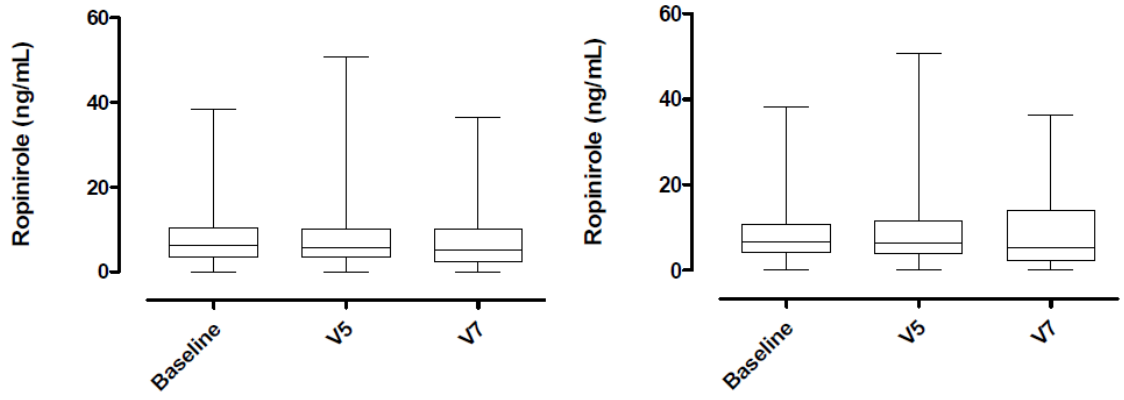


Source: Report BIA-91067-AntiPD001 Figure 7 and Figure 8. V = visit.

Ropinirole

In a pooled analysis of subjects with PD from the Phase 3 studies, (BIA-91067-301 and BIA-91067-302), Ropinirole concentrations were assessed at baseline (ie, randomization; N=115 subjects), Visit 5 (up to 49 days after baseline; N=111 subjects), and Visit 7 (up to 95 days after baseline; N=101 subjects) for subjects receiving 25 or 50 mg qd OPC (combined analysis) and subjects receiving only 50 mg qd OPC (N=59, 58, and 51 for randomization, Visit 7, and Visit 9, respectively). There were no relevant differences in mean pooled plasma concentrations of ropinirole when comparing Visits 5 and 7 with baseline in the combined 25/50 mg OPC group or the 50 mg OPC group (Figure 11).

Figure 11: Mean Pooled Plasma Ropinirole Concentrations per Visit for the 25 and 50 mg OPC Dose Levels Combined (Left) and the 50 mg OPC Dose Level Alone (Right) (Report BIA-91067-AntiPD001)

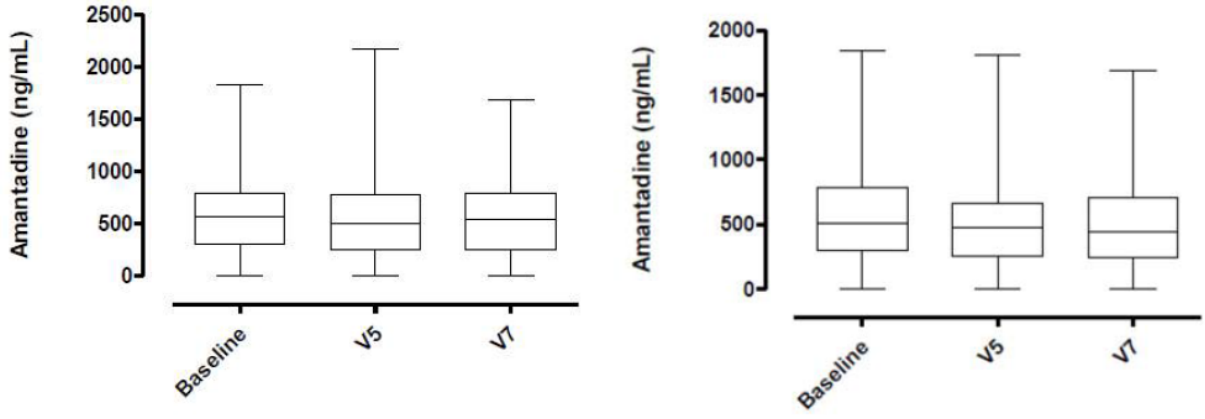


Source: Report BIA-91067-AntiPD001 Figure 11 and Figure 12. V = visit.

Amantadine

In a pooled analysis (Report BIA-91067-AntiPD001) of subjects with PD from the Phase 3 studies (BIA-91067-301 and BIA-91067-302), amantadine concentrations were assessed at baseline (ie, randomization; N=116 subjects), Visit 5 (up to 49 days after baseline; N=113 subjects), and Visit 7 (up to 95 days after baseline; N=98 subjects) for subjects receiving 25 or 50 mg qd OPC (combined analysis) and subjects receiving only 50 mg qd OPC (N=60, 56, and 51 for randomization, Visit 7, and Visit 9, respectively). There were no relevant differences in mean pooled plasma concentrations of amantadine when comparing Visits 5 and 7 with baseline in the combined 25/50 mg OPC group or the 50 mg OPC group (Figure 12).

Figure 12: Mean Pooled Plasma Amantadine Concentrations per Visit for the 25 and 50 mg OPC Dose Levels Combined (Left) and the 50 mg OPC Dose Level Alone (Right) (Report BIA-91067-AntiPD001)



Source: Report BIA-91067-AntiPD001 Figure 3 and Figure 4. V = visit.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

Four formulations were used during the clinical development program of OPC. The non-micronized, micronized, registrational[40], and the to-be-marketed formulations. The non-micronized formulation was used in the early Phase 1 trials as well as in the Phase 2 trials. The micronized formulation was used in some Phase 1 trials as well as in the pivotal Phase 3 trials. The registrational formulation is the commercial-scale lots of the micronized formulation. A bridging study was conducted for the micronized and registrational formulations. The proposed US to-be-marketed formulation is identical to that of the registrational formulation, with 1 minor change. One of the colorants was removed from the body of the capsule used for the registrational formulation, resulting in a slightly different color for the proposed US commercial capsules. No in vivo bridging is required between registrational and US to-be-marketed formulations.

Bridging micronized formulation to the non-micronized formulation (i.e., Phase 1/Phase 2 to Phase 3 formulation):

The OPC formulation used for initial Phase 1 studies and the two Phase 2 studies was the non-micronized formulation. The relative bioavailability of the micronized formulation was compared with the non-micronized formulation in Study BIA-91067-120. OPC C_{max}, AUC_{last} and AUC_{inf} were lower by approximately 56%, 50% and 43%, respectively, following administration of the OPC non-micronized formulation relative to the micronized formulation.

[40] Commercial-scale lots of each strength of Opicapone Capsules manufactured in Q1 2012 at the proposed commercial manufacturing site (b) (4)

Bridging the registrational formulation to the Phase 3 clinical trial formulation:

The pivotal Phase 3 studies used three strengths of a micronized formulation (5, 25, 50 mg capsules). The proposed commercial drug products for opicapone in US market is 25 mg and 50 mg capsules, (b) (4) The proposed commercial strengths (i.e. 25 mg and 50 mg) are not proportionally similar in composition. As a result of these changes, an in vivo bioequivalence study was conducted to bridge the proposed 2 commercial strengths to the Phase 3 clinical trial (micronized) formulation.

Study BIA-91067-119 was a Phase 1 randomized, single-dose, open-label, 3-part, 2-way crossover study to investigate the relative bioavailability and bioequivalence of the clinical micronized and the registrational formulations of OPC at different dose strengths. Subjects received single, oral doses of 5 mg, 25 mg, or 50 mg OPC in Parts 1, 2, and 3 of the study, respectively. In each part, for 2 consecutive treatment periods, subjects received single doses of OPC administered as the micronized or registrational formulations in random sequence. Since the 5 mg capsule strength is not intended for marketing, we don't include this result in this review.

Results of this study is summarized in Table 3. The 50 mg registrational formulation was bioequivalent to the micronized formulation for all C_{max} and AUC parameters. The 25 mg registrational formulation was bioequivalent to the micronized formulation on the basis of AUC. However, the upper 90% CI for C_{max} slightly missed the 125% bioequivalence criteria. This difference is not expected to be of any clinical relevance.

It is noted that the proposed US to-be-marketed formulation is identical to that of the registrational formulation, with 1 minor change. One of the colorants was removed from the body of the capsule used for the registration formulation, resulting in a slightly different color for the proposed US commercial capsules. As such Study BIA-91067-119 can serve as the pivotal PK bridge study bridging the Phase 3 clinical trial formulation to the to-be-marketed formulation.

Table 3: Pharmacokinetic Parameters of OPC after Single Doses of OPC 25 mg, and 50 mg Administered as the Micronized Formulation Compared with the Registrational Formulation (Study BIA-91067-119)

Parameter	Registrational Formulation (Test)	Micronized Formulation (Reference)	Test/Reference GMR% (90% Confidence Interval)
25 mg OPC			
N	28	27	
C_{max}, ng/mL	471.0 (42.6)	424.5 (36.8)	110.5 (96.7; 126.2)
AUC_{last}, ng.h/mL	1270 (41.5)	1137 (37.6)	110.9 (99.5; 123.6)
AUC_{inf}, ng.h/mL	1277 (39.4)	1321 (25.0)	97.6 (89.3; 106.7)
50 mg OPC			
N	28	28	
C_{max}, ng/mL	802.9 (39.6)	756.2 (38.4)	106.2 (96.5; 116.8)
AUC_{last}, ng.h/mL	2161 (45.1)	2043 (45.7)	105.8 (97.5; 114.8)
AUC_{inf}, ng.h/mL	2246 (45.4)	2244 (40.8)	101.9 (93.9; 110.7)

Source: Study BIA-91067-119, Table 13 (page 59), Table 14 (page 61), Table 16 (page 64), Table 17 (page 65).

The Office of Study Integrity and Surveillance (OSIS) conducted a routine site inspection for the pivotal PK bridging study BIA-91067-119 for the bioanalytical and the clinical sites. The analytical portion of Study BIA 9-1067-119 was conducted at (b) (4) The OSIS inspection for the bioanalytical site did not observe any objectionable conditions and the final inspection classification is No Action Indicated (NAI) (Ref. Surveillance inspection of (b) (4) review report, by Dr. Hasan A. Irier, in DARRTS dated Feb 3rd, 2020).

On the other hand, OSIS inspection for the clinical site for Study BIA-91067-119, conducted at Biotrial Rennes, Rennes, France, recommended that the data from study BIA-91067-119 are not reliable to support a regulatory decision. The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report. At the conclusion of the inspection, investigator Tawny L. Colling reported objectionable conditions due to the non-availability of reserve samples for the test and reference products at the study site. No other issues were identified (Ref. Surveillance inspection of Biotrial Rennes, Rennes, France review report, by Dr. Sripal Reddy Mada, in DARRTS dated Feb 26th, 2020).

In response to the OSIS findings of the non-availability of the reserve samples, Biotrial stated that they are aware of FDA's regulatory requirements for BA/BE studies, including 21 CFR 320.38 and 320.63. However, the study protocol was written in compliance with EMA regulations because the sponsor, Bial, is located in Portugal and the study was conducted at a French clinical site. Biotrial stated that Bial instructed them to follow the EU regulations and guidelines when they contracted

with Biotrial to conduct study BIA-91067-119 in 2014. After the EU approval, the sponsor authorized the destruction of the samples on May 4, 2017, without consideration of the licensing agreement on February 15, 2017 with Neurocrine Biosciences (the NDA applicant).

The study site reported to OSIS that the reserve samples were discarded after opicapone received European Union Marketing Authorization in 2016 and that they followed EU regulations (Ref. Bioequivalence Establishment Inspection Report Review, by Dr. Sripal Reddy Mada, in DARRTS dated Feb 26th, 2020). Biotrial stated that only the reference samples from the batches used in study BIA-91067-119 were retained by Bial in their Portugal facilities. The sponsor, Bial, acknowledges that the FDA's BE reserve sample regulation was not followed, and that the decision process to authorize the sample destruction was inadequate. Bial currently understands that personnel within the organization to which the product is licensed must review and approve all destruction requests and authorizations, before any action. The current NDA applicant, Neurocrine Biosciences, indicated that they became aware of the lack of reserve samples on the second day of the OSIS inspection and acknowledged their obligation to assure proper retention of drug samples for all studies (Ref. Surveillance inspection of Biotrial Rennes, Rennes, France review report, by Dr. Sripal Reddy Mada, in DARRTS dated Feb 26th, 2020).

In light of OSIS findings, and since the only issue is related to independent verification of the test (registrational formulation) and reference (Phase 3 formulation) products used in the PK bridging study, the review team compared the PK of OPC following administration of the Phase 3 clinical trial formulation (micronized) and the registrational formulation from available Phase 1 studies to gain insights on the consistency of the results between studies. This may provide supportive evidence for Study BIA-91067-119 PK findings. While Study BIA-91067-119 was the only study that used both formulations in a crossover manner, there were 6 Phase 1 studies that assessed the PK of OPC following 50 mg single dose administration of either the Phase 3 clinical trial formulation (Studies BIA-91067-120, BIA-91067-125, BIA-91067-126, NBI-OPC-1705, NBI-OPC-1707) or the registrational formulation (Study BIA-91067-121). In addition, 2 out of these 6 studies also assessed the PK of OPC following 25 mg single dose administration of either the Phase 3 clinical trial formulation (Study BIA-91067-126) or the registrational formulation (Study BIA-91067-121). Summary of the PK parameters (C_{max} and AUC_{inf}) from these studies for both formulations for the 50 mg and 25 mg strengths are summarized in Table 4 and Table 5, respectively.

In general, with cross-study comparisons, the PK results from these studies were in agreement with the PK bridging study BIA-91067-119. Specifically, findings from 4 out of 6 of these studies supported the findings from Study BIA-91067-119 for the 50 mg strength[41]. Study BIA-91067-121

[41]Notably, Study BIA-91067-126 showed a consistent doubling of overall OPC exposure across both the 25 mg, and 50 mg dosing strengths using the micronized formulation. The reason for such consistent increase in exposure is not clear and may be due to random variability or due to differences in the bioanalytical assay. Interestingly, Studies BIA-91067-121, BIA-91067-120, BIA-91067-125 were analyzed using the same bioanalytical assay as the one used for Study BIA-

showed consistent PK results with the registrational formulation period form Study BIA-91067-119 and established the dose proportionality between the 25 mg and the 50 mg strengths for the registrational formulation. Notably, EMA had considered Study BIA-91067-119 during the review and subsequent approval of opicapone in 2016[42]. Communication with EMA indicated that the site where the study was conducted was routinely inspected but no specific inspection for Study BIA-91067-119 was conducted by EMA.

Considering the following facts: 1) The study protocol compliance was verified by the OSIS inspector, including the documentation of test and reference product administration. The only issue from the OSIS inspection is the non-availability of reserve sample for the test and reference products used in the study. , 2) A cross-study comparison using PK data from Phase 1 studies included in the NDA that used Phase 3 formulation and the registrational formulation suggests the results from study BIA-91067-119 as reliable, and 3) acceptance of the results from Study BIA-91067-119 by EMA in 2016 to support marketing authorization for ONGENTYS in Europe, based on routine Biotrial site inspection and no specific inspection for this study, , the review team concluded that bridging results from Study BIA-91067-119 is acceptable.

91067-119 (Bioanalytical Method Study Report: (b) (4)_S_12036). The bioanalytical method used for Studies NBI-OPC-1705, NBI-OPC-1707 were reported in the Bioanalytic Method Study Report: (b) (4)-W3-679 for both studies. The bioanalytical method used for Study BIA-91067-126 was used for other Phase 1 studies that utilized a nonmicronized formulation (Bioanalytical Method Study Report: (b) (4)_S_06077)[41]. Results from these Phase 1 studies that were analyzed with the bioanalytical method summarized in (b) (4)_S_06077 were compared with results from Studies BIA-91067-120 which utilized the nonmicronized formulation (2x25 mg) and utilized the same bioanalytical method that was used for studies BIA-91067-121, BIA-91067-125, and Study BIA-91067-119 ((b) (4)_S_12036). Notably, data from the nonmicronized formulation 50 mg showed 50-70% higher Cmax but only 10-30% higher AUC of OPC when data was analyzed according to the bioanalytical method reported in (b) (4)_S_06077 as compared to the bioanalytical method reported in (b) (4)_S_12036. Therefore, the inconsistency of OPC PK parameter following the micronized formulation from Study BIA-91067-126 may not be fully explained by differences in the analytical method utilized.

[42] https://www.ema.europa.eu/en/documents/assessment-report/ongentys-epar-public-assessment-report_en.pdf

Table 4: Pharmacokinetic Parameters of OPC after Single Doses of OPC 50 mg Administered as the Micronized Formulation or as the Registrational Formulation

Study	Main Objective	Parameter	50 mg Micronized Formulation Geometric Mean (% CV)	50 mg Registrational FormulationGeometric Mean (% CV)
BIA-91067-119	Pivotal PK Bridging	C_{max}	756.2 (38)	802.9 (40)
		AUC_{inf}	2244 (41)	2246 (45)
BIA-91067-121	Dose proportionality	C_{max}	-	828 (20)
		AUC_{inf}	-	2400 (45)
BIA-91067-120[1]	Relative BA study	C_{max}	750.1 (24)	
		AUC_{inf}	2324.1 (30)	
BIA-91067-125[2]	DDI-Paracetamol	C_{max}	895 (42)	
		AUC_{inf}	2451 (36)	
BIA-91067-126[3]	Effect of ethnicity	C_{max}	1540 (32)	
		AUC_{inf}	3756 (46.2)	
NBI-OPC-1705[4]	Hepatic impairment	C_{max}	605 (39)	
		AUC_{inf}	1650 (42)	
NBI-OPC-1707[5]	DDI-Quinidine	C_{max}	804 (32)	
		AUC_{inf}	2136 (27)	
[1]data were taken from the Phase 3 (micronized) formulation arm [2]data were taken from OPC only period [3]data were taken from the Caucasian population [4] data were taken from the normal arm [5]data were taken from OPC only period				

Source: Reviewer Analysis

Table 5: Pharmacokinetic Parameters of OPC after Single Doses of OPC 25 mg Administered as the Micronized Formulation or as the Registration Formulation

Study	Main Objective	Parameter	25 mg Micronized Formulation Geometric Mean (% CV)	25 mg Registrational Formulation Geometric Mean (% CV)
BIA-91067-119	Pivotal PK Bridging	C_{max}	424.5 (36.8)	471 (43)
		AUC_{inf}	1321 (25)	1277 (39)
BIA-91067-121	Dose proportionality	C_{max}		526 (42)
		AUC_{inf}		1441 (39)
BIA-61067-126[1]	Effect of ethnicity	C_{max}	794 (49.3)	
		AUC_{inf}	2039 (39.1)	
[1]data were taken from the Caucasian population				

Source: Reviewer Analysis

Bridging the to-be-marketed formulation to the registrational formulation:

For both the 25 mg and 50 mg capsule strengths, the proposed US to-be-marketed formulation uses an identical (b) (4) to that used for the registrational formulation. As mentioned above, the registrational formulation and the proposed to-be-marketed formulation differ only in the color of the gelatin capsule shells. This minor difference between the formulations is not expected to affect the dissolution profile or relative bioavailability of the proposed US commercial product.

Thus, in summary, the to-be-marketed formulation is adequately bridged to the clinical trial formulations. This decision is based on the available data within the application that showed internal consistency with the findings from study BIA-91077-119.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

PK analyses included in this submission used validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) assays for the quantification of OPC and its metabolites in both plasma and urine. All sample analyses were conducted in accordance with FDA Guidance for Industry, Bioanalytical Method Validation; 2001). The applicant submitted reports of 17 bioanalytical assays that were developed and validated for the analysis of OPC and its metabolites in plasma and urine. Thirteen validations were performed with OPC and/or its metabolites in plasma. In this review we report the assay validation for OPC in plasma for Study BIA-91067-119 (i.e. the pivotal formulation bridging study). Results of OPC assay validation in plasma were included in (b) (4)_S_12036 report.

Details of the method performance characteristics, including selectivity, lower limit of quantitation, precision, accuracy, extraction recovery, dilution factor, matrix effects, in-process stability, and frozen stability for quantitation of OPC for Study BIA-91067-119 are provided in Table 6.

Table 6: Summary of the Bioanalytical Method Validation

Parameter	**Value**
Analyte	OPC
Internal standard (IS)	BIA 9-1067-13C6
Limit of quantitation (ng/mL)	10-2500 ng/mL
Calibration curve regression model, weighing factor and correlation coefficient	Quadratic, 1/X, ≥0.9992
Precision and accuracy	
QC inter-run precision range (%)	4-5.7%
QC inter-run accuracy range (%)	92.7-96%
QC Intra-run precision range (%)	1.3-7.7%
QC Intra-run accuracy range (%)	91.7-97.5%
Average recovery of drug (%)	86.5-94.5%
Selectivity	Up to 7.1%
Stability	
Stability in matrix (QC1, QC3)	Bench-top: 20 hours at 20 °C Freeze/thaw: 3 cycles -25/20 °C Long-term: 195 days at -25 °C Long-term: 118 days at -85 °C
Stability after sample processing	Post-preparative: 40 hours at 8 °C Re-injection reproducibility: 7 hours at 8 °C

4.2 Population PK Analyses

4.2.1. Sponsor's Population PK analysis:

A population pharmacokinetic (Pop-PK) model was developed to support dose adjustment justification as part of the OPC new drug application (NDA).

Objective:

The goal of this current analysis is to describe the PK of OPC in adult healthy volunteers and PD patients. This overall goal has been achieved through the following sub-objectives:

- To build a Pop-PK model in order to describe the plasma concentration of POC over time
- To assess the impact of intrinsic and extrinsic factors (e.g. body weight, age, formulation, food, race, liver impairment, creatinine clearance) on the PK of OPC in adults
- Evaluate the labeling statements based on Pop-PK analysis

Labeling statements in Section 12.3 of the proposed label based on population

pharmacokinetic analyses:

(b) (4)

Method:

Pop-PK model describing OPC PK in healthy volunteers and PD patients after single or multiple dose administration of OPC formulations was developed using NONMEM (Version 7.3).

Data

A Pop-PK model for OPC was developed using pooled data from 21 clinical studies including 18 Phase 1 studies in healthy subjects and 3 studies (1 Phase 1 and 2 Phase 2) in patients with PD. Table 7 summarizes the main design aspects of the studies that were included in the analyses. A total of 9686 quantifiable OPC concentrations from 724 subjects given OPC under fasting conditions were included in the Pop-PK analysis.

Missing PK data, time, covariates

Missing PK concentrations were excluded from the analysis. Plasma concentrations determined to be below the limit of quantification (BLQ) were retained in the analysis dataset but were excluded from the analysis. Actual dates and times of pharmacokinetic samples and doses were used whenever possible. If actual dates and times were missing then it was assumed that samples were collected according to the protocol specified times without error (i.e., nominal times were utilized). If nominal times were not available, then samples with missing times were excluded. For time-invariant covariates, values collected from the baseline visit (i.e., the visit immediately before the first dosing of the study medication) were used. Missing baseline covariate data were imputed using covariate values from a visit that occurs earlier than the baseline visit (e.g., the screening visit). If screening values were also missing, then the nearest post-baseline covariate value was used.

Modeling approach

First, a base model, including the assessment of the random effects structure, was identified. Once a suitable base model had been identified, a full model was evaluated by including pre-specified covariates simultaneously in a single model. A covariate reduction procedure was performed to identify a parsimonious preliminary final model. This was performed by using a stepwise backward elimination using the likelihood ratio test with inclusion criteria of $\Delta OFV < 10.8$ ($p<0.001$). The predictive performance of the preliminary final model was evaluated using a visual predictive check. The preliminary final model was accepted as the final model if the predictive performance was adequate; otherwise, the preliminary final model would undergo model refinement until the predictive performance was adequate.

Model development was carried out using first order conditional estimation with interaction (FOCE-I).

Table 7: Summary of the Characteristics of the Studies used for Pop-PK Analyses

Study	Phase	Population / No. Subjects Randomized	Study Design	Treatment Regimen	PK Sampling Scheme[a]
BIA-91067-101	1	Healthy subjects 64 males (64 completed) (8 per group) Age: 19-45 years	SAD Study: Single-center, randomized, double-blind, PBO-controlled, ascending single dose, PK and COMT inhibition study	Single dose of PBO or nonmicronized OPC API: 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg	Pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60 and 72 h post-dose
BIA-91067-102	1	Healthy subjects 34 males (32 completed) (8 per group) Age: 20-45 years	MAD study: Single-center, randomized, double-blind, PBO-controlled, ascending multiple dose, PK-PD study	PBO or nonmicronized OPC API qd for 8 days: 5 mg, 10 mg, 20 mg, 30 mg	Day 1: Pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dose (24 h = Day 2 pre-dose) Pre-dose on Days 2 to 7 inclusive Day 8: Pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 h post-dose
BIA-91067-104[b]	1	Healthy subjects 12 males (11 completed) Age: 18-43 years	Single-center, randomized, open-label, single-dose, 2-period, 2-sequence, crossover, comparative bioavailability, food-effect study	Single doses of nonmicronized OPC API: 50 mg in each period under fasting or fed conditions	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dose
BIA-91067-105	1	Healthy subjects 24 males (24 completed): 12 non-elderly Age: 19-38 years 12 elderly Age: 65-78 years	Single-center, non-randomized, open-label, parallel-group, multiple-dose, steady-state PK, age-effect study	30 mg nonmicronized OPC API qd for 7 days	Day 1 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dose Day 3 to Day 6 at pre-dose (trough levels) Day 7 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 h post-last dose
BIA-91067-106	1	16 subjects (16 completed): 8 subjects with hepatic impairment (7M/1F) Age: 37-56 years 8 healthy subjects (7M/1F) Age: 38-56 years	Multicenter, non-randomized, open label, parallel-group, single-dose, PK and COMT inhibition study in subjects with moderate chronic hepatic impairment and in matched healthy subjects	Single dose of nonmicronized 50 mg OPC API	Pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60 and 72 h post-dose.
BIA-91067-107	1	Healthy subjects 16 males (14 completed) Age: 25-43 years	Single-center, randomized, double-blind, PBO-controlled, 4-period crossover, single-dose, PK-PD interaction study with OPC and levodopa/benserazide	Single doses of PBO or nonmicronized OPC API (25 mg, 50 mg, or 100 mg) in each period concomitantly with 100/25 mg immediate-release levodopa/benserazide	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48 and 72 h post-dose.
BIA-91067-108	1	Healthy subjects 16 males (14 completed) Age: 18-45 years	Single-center, randomized, double-blind, PBO-controlled, 4-period crossover, single-dose, PK-PD interaction study with OPC and levodopa/carbidopa	Single doses of PBO or nonmicronized OPC API (25 mg, 50 mg, or 100 mg) in each period concomitantly with 100/25 mg immediate-release levodopa/carbidopa	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48 and 72 h post-dose
BIA-91067-109	1	Healthy subjects 22 males (20 completed) Age: 23-36 years	Single-center, randomized, double-blind, PBO-controlled, 4-period crossover, single-dose, PK-PD interaction study with OPC and levodopa/benserazide	Single doses of PBO or nonmicronized OPC API (25 mg, 50 mg, or 100 mg) in each period concomitantly with 100/25 mg controlled-release levodopa/benserazide	Pre-dose and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48 and 72 h post-dose
BIA-91067-110	1	Healthy subjects 12 males (11 completed) Age: 29-43 years	Single-center, randomized, double-blind, PBO-controlled, 4-period crossover, single-dose, PK-PD interaction study with OPC and levodopa/carbidopa	Single doses of PBO or nonmicronized OPC API (25 mg, 50 mg, or 100 mg) in each period concomitantly with 100/25 mg controlled-release levodopa/carbidopa	Pre-dose and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48 and 72 h post-dose
BIA-91067-111	1	Healthy subjects 64 subjects (33M/31F) (61 completed) Age: 18-56 years	Thorough QT study: Single-center, randomized, PBO-controlled (double-blind) and active-controlled (open-label), 4-period crossover, cardiac repolarization study	Single doses of PBO, 400 mg moxifloxacin, or nonmicronized OPC API (50 mg or 800 mg) in each period	Pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 h post-dose

Study	Phase	Population / No. Subjects Randomized	Study Design	Treatment Regimen	PK Sampling Scheme[a]
BIA-91067-114	1	Healthy subjects 82 subjects (41M/41F) (80 completed) Age: 19-44 years	Single-center, randomized, double-blind, PBO- and active-controlled, parallel-group, multiple-dose study to investigate the effect of OPC on levodopa PK compared to PBO and ENT	Days 1-7: Group 1 received PBO at all dosing times Groups 2-4 received nonmicronized OPC API (5 mg, 15 mg, or 30 mg) as the first dose of each day and PBO at the other 3 daily dosing times Group 5 received PBO as the first dose of each day and 200 mg ENT at the other 3 daily dosing times Day 8: Group 1 received PBO as the first dose of the day and approximately 1 hour later PBO concomitantly with a single dose of 100/25 mg standard-release levodopa/carbidopa Groups 2-4 received nonmicronized OPC API (5 mg, 15 mg, or 30 mg) as the first dose of the day and approximately 1 hour later PBO concomitantly with a single-dose of 100/25 mg standard-release levodopa/carbidopa Group 5 received PBO as the first dose of the day and approximately 1 hour later 200 mg ENT concomitantly with a single-dose of 100/25 mg standard release levodopa/carbidopa	Groups 2-4 (OPC treatments): Days 1, 3, 5 and 7: Prior to the first dose of the day (OPC). Day 8: Prior to and 0.5 h after the first dose of the day (OPC); prior to and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h after the second dose of the day (PBO) which was given approximately 1 h after the first dose Group 1 and Group 5 (PBO and ENT treatments, respectively) were not included.
BIA-91067-117	1	Healthy subjects 18 subjects (10M/8F) (16 completed) Age: 19-44 years	Single-center, randomized, open-label, 4-period crossover, single-dose, PK study with levodopa/carbidopa	Single doses of 50 mg nonmicronized OPC API alone, or concomitantly with 100/25 mg levodopa/carbidopa immediate-release, or 1 hour before the 100/25 mg immediate-release levodopa/carbidopa dose, or 100/25 mg immediate-release levodopa/carbidopa alone per study period	Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 h post-dose

Study	Phase	Population / No. Subjects Randomized	Study Design	Treatment Regimen	PK Sampling Scheme[a]
BIA-91067-118	1	Healthy subjects 52 subjects (25M/27F) (48 completed) (12 per group) Age: 25-45 years	Single-center, randomized, double-blind, PBO-controlled, multiple-dose study to investigate levodopa PK in steady-state conditions with levodopa/carbidopa and levodopa/benserazide	PBO or nonmicronized OPC API (5 mg, 15 mg, or 30 mg) qd for 28 days, concomitantly with 100/25 mg immediate-release levodopa/carbidopa on Day 21 and 100/25 mg immediate-release levodopa/benserazide on Day 28	Pre-dose on Days 1, 4, 7, 10, 14, 17, 19, 24 and 26 Days 21 and 28: Pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose
BIA-91067-119	1	Healthy subjects 85 subjects (48M/37F) (83 completed) (28-29 subjects per group) Age: 18-45 years	Single-center, randomized, open-label, 3-part, 2-period crossover, single-dose study to investigate the bioavailability and bioequivalence of different formulations of OPC (micronized API formulation and to-be-marketed formulation) in each of 5, 25, and 50 mg dose levels	Each subject received a single dose of micronized OPC API in the Phase 3 formulation in 1 treatment period or micronized OPC API in the to-be-marketed formulation in the other treatment period. Part 1 subjects received OPC at a 5 mg dose level, Part 2 subjects at 25 mg dose level, and Part 3 subjects at a 50 mg dose level	Pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose
BIA-91067-120	1	Healthy subjects 28 subjects (14M/14F) (28 completed) (14 per group) Age: 18-45 years	Single-center, randomized, open-label, 2-period crossover, single-dose study to investigate the bioavailability and bioequivalence of 50 mg OPC nonmicronized API formulation and 50 mg OPC clinical micronized	Single doses of 50 mg nonmicronized OPC API formulation capsule in 1 treatment period and 50 mg micronized OPC API formulation capsule in the other treatment period	Pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose
BIA-91067-121	1	Healthy subjects 56 subjects (28M/28F) (55 completed) (28 per group) Age: 19-45 years	Single-center, randomized, open-label, 2-sequence, 2-period crossover, single-dose study to investigate the bioequivalence between 5 x 5 mg and 1 x 25 mg, and between 2 x 25 mg and 1 x 50 mg dose forms of OPC	Each subject in Group 1 received a single dose of 25 mg micronized OPC API as 5 x 5 mg OPC or 1 x 25 mg OPC, and each subject in Group 2 received a single dose of 50 mg micronized OPC API as either 2 x 25 mg OPC or 1 x 50 mg OPC	Pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 h post-dose

Study	Phase	Population /No. Subjects Randomized	Study Design	Treatment Regimen	PK Sampling Scheme[a]
BIA-91067-123	1	Healthy subjects 74 subjects (36M/38F) (72 completed) (18 per group) Age: 18-45 years	Single-center, randomized, double-blind, PBO-controlled, multiple-dose study to investigate levodopa PK in steady-state conditions with levodopa/carbidopa and levodopa/benserazide	PBO or nonmicronized OPC API (5 mg, 15 mg, or 50 mg) qd for 18 days, with 100/25 mg levodopa/carbidopa on Day 11 and 100/25 mg levodopa/benserazide on Day 18 after the OPC/PBO dose	Pre-dose on Days 1, 4, 7, 10, 13, 15 and 17. Days 11 and 18: Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose
BIA-91067-126	1	Healthy subjects 105 subjects (103 completed): (54 Japanese subjects) Age: 20-65 years (51 Caucasian subjects) Age: 22-65 years	Japanese bridging study: Single-center, randomized, double-blind, placebo-controlled, parallel-group, multiple ascending dose, PK-PD study in Japanese and Caucasian subjects	PBO or micronized OPC API (5 mg, 25 mg, or 50 mg) qd for 10 days	Day 1: Pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 h post-dose Day 10: Pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, 96, 120 and 144 h post-dose.
BIA-91067-128[c]	1	Healthy subjects 28 subjects (14M/14F) (28 completed) Age: 18-44 years	Food effect study: Single-center, open-label, single-arm study in healthy subjects to investigate the effect of food on COMT activity after repeated doses of OPC	Micronized OPC API 50 mg qd for 12 days in the evening under fasted conditions. On Day 10, micronized OPC API 50 mg qd 30 minutes after the start of a moderate meal.	Days 9 and 10: Pre-dose and at 0.5, 1, 2, 3, 4, 6, 12 and 24 h post-dose (Day 9 24 h post-dose = Day 10 pre-dose)
NBI-OPC-1706	1	PD patients 16 subjects	Open-label, multiple-dose study to investigate the effect of repeated doses of OPC on levodopa PK in subjects with PD	Micronized OPC API 50 mg qd for 14 days. Stable regimen of levodopa/carbidopa throughout study.	Day 1: Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 8, 10, 12, 16 and 24 h post-dose Day 7 and 13: Pre-dose Day 14: Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 8, 10, 12, 16, 24, 48, 72, 96 and 120 h post-dose.

Study	Phase	Population INo. Subjects Randomized	Study Design	Treatment Regimen	PK Sampling Scheme[a]
BIA-91067-201	2	PD patients 10 subjects (6M/4F) (9 completed) 42-70 years	Three-center, randomized, double-blind, placebo-controlled, 4-way crossover, single dose study to investigate the effect of OPC on levodopa PK, COMT activity, and motor response in PD patients treated with levodopa/DDCI	Nonmicronized OPC API (25, 50, or 100 mg) or placebo concomitantly with IR 100/25 mg levodopa/DDCI and IR 100/25 mg levodopa/DDCI alone.	Day 3 (OPC dosing day): Pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 h post-dose
BIA-91067-202	2	PD patients 40 subjects (20M/20F) (36 completed) 49-88 years	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study to investigate the effect of OPC on levodopa PK, COMT activity, and motor response in PD patients treated with levodopa/DDCI	Nonmicronized OPC API (5, 15, or 30 mg) or placebo qd for 21 to 28 days, 1 hour prior to morning levodopa/DDCI dose	Pre-dose and 1, 2, 4 and 6 h post-dose, on the day prior to the 2nd levodopa test at the end of the 21 to 28-day maintenance phase.

[a] Plasma samples for OPC concentration (PK data for OPC metabolites or other study medications were not included in the model)
[b] Study 104 data from both fed and fasted conditions were not included in the population PK model
[c] Study 128 data from the fed condition were not included in population PK model

OPC = opicapone; PD = Parkinson's disease; M = male; F = female; SAD = single ascending dose; MAD = multiple ascending dose; PBO = placebo; ENT = entacapone; API = active pharmaceutical ingredient; PK = pharmacokinetics; PK-PD = pharmacokinetic-pharmacodynamic; COMT = catechol-O-methyltransferase; qd = once daily; h = hour(s); DDCI = decarboxylase inhibitor (carbidopa or benserazide)

Source: Pop-PK report(2018-CP-198); page 17-22; Table 1.

Results:

Categorical and continuous covariate data for subjects in the Pop-PK analysis are summarized in Table 8.

Table 8: Covariate Summary

Variable	Category	Value
Continuous, Median (Range)		
Body weight (kg)	-	71 (43.1 - 110)
Age (years)	-	35 (18 - 84)
CLcr (mL/min)	-	110.1 (37 - 199.3)
Bilirubin (µmol/L)	-	12 (1.71 - 54)
Albumin (g/L)	-	45 (32.1 - 54.5)
AST (IU/L)	-	22 (9 - 148)
Categorical, N (%)		
Sex	Male	456 (63%)
	Female	268 (37%)
Race	White	557 (77%)
	Asian	43 (6%)
	Black	29 (4%)
OPC with levodopa/DDCI	Yes	290 (38%)[a]
	No	471 (62%)[a]
Formulation	Micronized	5 mg - 50 mg: 289 (38%)[b] 5 mg: 56
	Nonmicronized	5 mg - 1200 mg: 463 (62%)[b]
Evening Dose	Yes	99 (14%)
	No	625 (86%)
Disease State	Healthy	672 (93%)
	PD	52 (7%)

[a] Percent of total: 761 subjects (greater than the total of 724 subjects in the dataset), due to subjects administered levodopa/DDCI in a crossover design or on multiple occasions (Studies 117, 118 and 123). [b] Percent of total: 752 subjects (greater than the total of 724 subjects in the dataset), which includes 28 subjects administered both micronized OPC and nonmicronized OPC in a crossover design (Study 120)

CLcr = creatinine clearance, AST = aspartate aminotransferase, DDCI = dopa decarboxylase inhibitor (carbidopa or benserazide); OPC = opicapone

Source: Pop-PK report; page30-31; Table 4

Base Model:

The PK of OPC was adequately described by a one-compartment model with 1 transit absorption compartment and first-order elimination. The equations defining the base PK model are listed below:

$$CL/F = \theta_1 \cdot \exp(\eta_1)$$

$$V2/F = \theta_2 \cdot \exp(\eta_2)$$

$$KA = \theta_3 \cdot (1 + Micro \cdot \theta_6) \cdot \exp(\eta_3)$$

$$F1 = \left(\frac{Dose}{50}\right)^{\theta_7} \cdot (1 + Micro \cdot FLD50 \cdot \theta_8) \cdot (1 + Micro \cdot FLD25 \cdot \theta_9) \cdot (1 + Micro \cdot FLD05 \cdot \theta_{10})$$

where CL/F is the apparent clearance; V2/F is the apparent central distribution volume; KA is the transit absorption rate constant; θ1, θ2 and θ3 are the typical values of CL/F, V2/F and KA, respectively; F1 is the relative bioavailability; Dose is the administered dose of OPC and 50 is the reference dose of 50 mg; Micro is an indicator variable (=1 for micronized and =0 for nonmicronized); FLD50 is an indicator variable (=1 for 50 mg dose and =0 otherwise); FLD25 is an indicator variable (=1 for 25 mg dose and =0 otherwise); FLD05 is an indicator variable (=1 for 5 mg dose and =0 otherwise); θ6 is the fractional change in the typical value of KA for the micronized formulation; θ7 (gamma) is the exponent describing the change in F1 with dose, centered on the dose of 50 mg; θ8 is the fractional change in the typical value of F1 for micronized OPC 50 mg; θ9 is the fractional change in the typical value of F1 for micronized OPC 25 mg; θ10 is the fractional change in the typical value of F1 for micronized OPC 5 mg. The parameters η1, η2 and η3 are the subject-specific random effects for CL/F, V2 and KA, respectively.

Final Model:

The following equations describe the covariate-parameter relationships in the OPC final model:

$$CL/F = \theta_1 \cdot \left[\frac{BILI}{12}\right]^{\theta_{BILI}} \cdot (1 + Gender \cdot \theta_{15}) \cdot (1 + Asian \cdot \theta_{19}) \cdot exp(\eta_1)$$

$$V2/F = \theta_2 \cdot (1 + Asian \cdot \theta_{38}) \cdot exp(\eta_2)$$

$$KA = \theta_3 \cdot (1 + Micro \cdot \theta_6) \cdot (1 + Evening \cdot \theta_{11}) \cdot (1 + LDSim \cdot \theta_{12}) \cdot exp(\eta_3)$$

$$F1 = \left(\frac{Dose}{50}\right)^{\theta_7} \cdot (1 + Micro \cdot FLD50 \cdot \theta_8) \cdot (1 + Micro \cdot FLD25 \cdot \theta_9) \cdot (1 + Micro \cdot FLD05 \cdot \theta_{10}) \cdot (1 + LDSim \cdot \theta_{14})$$

where base model parameters as defined previously and additional parameters are defined as: BILI is the baseline total bilirubin; θBILI is the power to describe the relationship between baseline total bilirubin and CL/F centered on the median total bilirubin of 12 µmol/L; Gender is an indicator variable (=1 if female and =0 if male); Asian is an indicator variable (=1 if Asian race and =0 otherwise); Evening is an indicator variable (=1 if evening dosing and =0 otherwise); LDsim is an indicator variable (=1 if simultaneous co-administration of levodopa/DDCI [either levodopa/carbidopa or levodopa/benserazide] and =0 otherwise); θ15 is the fractional change in the typical value of CL/F for female subjects; θ19 is the fractional change in the typical value of CL/F for Asian subjects; θ38 is the fractional change in the typical value of V2/F for Asian subjects; θ11 is the fractional change in the typical value of KA for evening dosing; θ12 is the fractional change in the typical value of KA for simultaneous levodopa/DDCI administration with OPC; θ14 is the fractional change in the typical value of F1 for simultaneous levodopa/DDCI administration with OPC.

The PK parameter estimates for the Pop-PK final model are provided in Table 9.

Table 9: Parameter Estimates for the Final Population Pharmacokinetic Model

Theta	Parameter	Estimat	ASE	RSE	95%CI	Units
1	CL/F	37.6	0.88	2.4	(35.9; 39.3)	L/hr
2	V2/F	49.7	1.68	3.4	(46.4; 53)	L
3	KA	1.24	0.039	3.2	(1.16; 1.32)	hr-1
6	MICRO ON KA	0.245	0.050	20.	(0.146; 0.343)	
7	DOSE GAMMA ON	-0.288	0.009	-3	(-0.306; -0.27)	mg
8	MICRO 50 MG ON	0.681	0.055	8.2	(0.572; 0.79)	
9	MICRO 25 MG ON	0.609	0.073	12	(0.466; 0.753)	
10	MICRO 05 MG ON	0.106	0.065	61.	(-0.0221;	
11	EVENING ON KA	-0.595	0.031	-5.2	(-0.656; -	
12	LDOPA SIMUL ON	-0.408	0.032	-7.8	(-0.471; -	
14	LDOPA SIMUL ON	0.353	0.052	14.	(0.25; 0.456)	
15	GENDER ON CL/F	-0.138	0.028	-20.8	(-0.194; -	

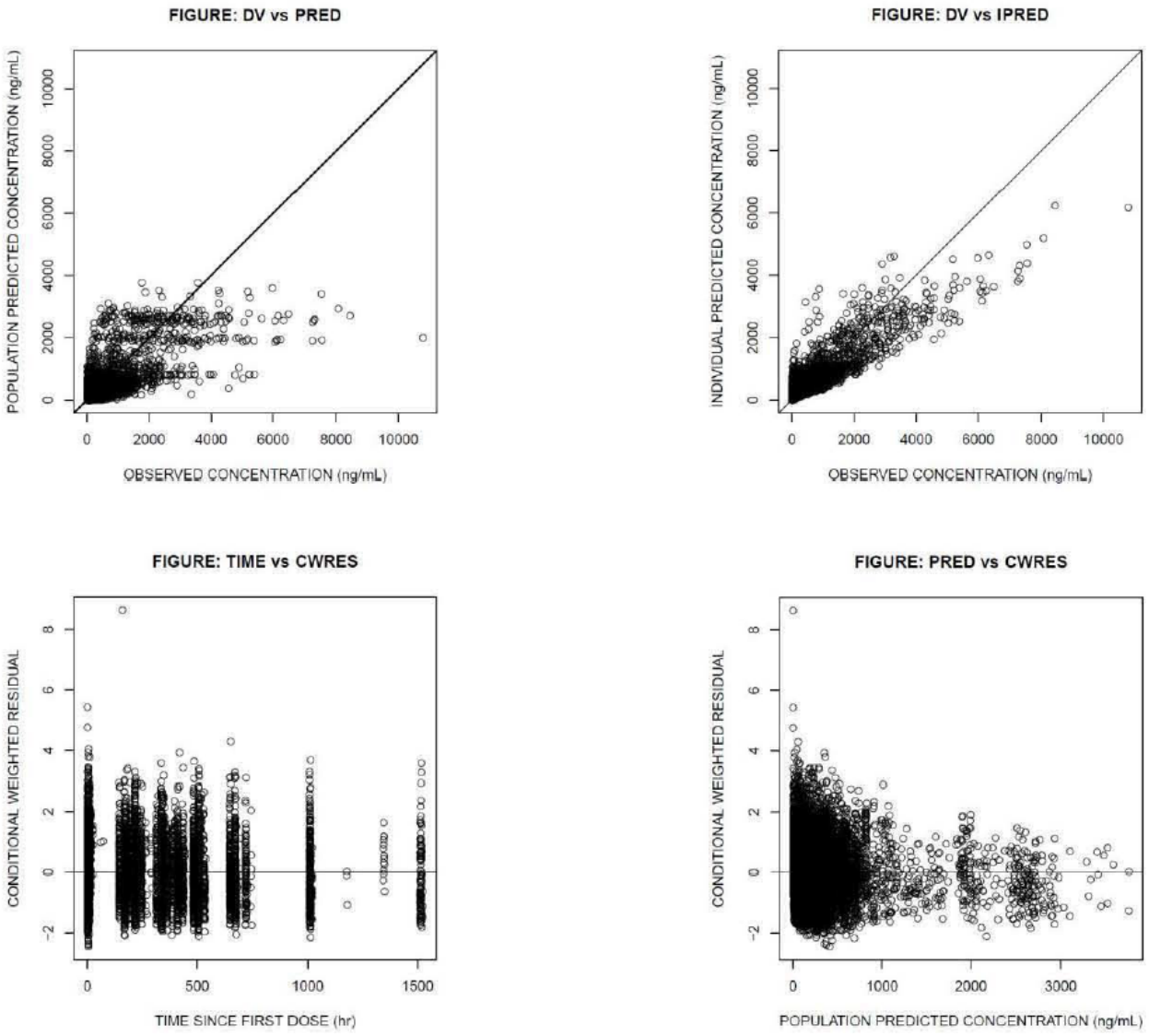
19	ASIAN ON CL/F	-0.307	0.0446	-14.4	(-0.394; -	
23	BILI ON CL/F	-0.116	0.0341	-29.3	(-0.183; -	
38	ASIAN ON V2/F	-0.389	0.0634	-16.2	(-0.514; -	
RE						
PROP		55.6	0.57	1	(54.5; 56.7)	%
ADD		11.5	0.391	3.4	(10.7; 12.3)	ng/mL
IIV						
CL/F		36.9			(34.5; 39.2)	CV%
V2/F		48.3			(42.6; 53.3)	CV%
KA		52.2			(48.4; 55.7)	CV%

ASE = asymptotic standard error; RSE = relative standard error; CI = confidence interval; CV% = percent coefficient of variation; RE = residual error; IIV = interindividual variability; OFV = objective function value; CL/F = apparent clearance; V2/F = apparent central distribution volume; KA = transit absorption rate constant; MICRO = micronized formulation; GAMMA = exponent describing the change in F1 with dose, centered on the dose of 50 mg; LDOPA = levodopa/DDCI (levodopa/carbidopa or levodopa/benserazide); SIMUL = simultaneous administration; BILI = total bilirubin.

Source: Pop-PK report; page 42/43; Table 9.

Goodness of fit plots for the final model are illustrated in Figure 13.

Figure 13: Final Model Goodness of Fit Plots



Source: Pop-PK report (2018-CP-198); page 44; Figure 5.

Reviewer Comment:

Overall, the final model demonstrated appropriate agreement between predicted and observed data values. The reviewer checked if there is model misspecification by study or specific covariates such as gender or race. However, it didn't seem to be the case. Moreover, the CWRES are randomly scattered around the predicted range and across time. Overall, the diagnostic plots of residuals indicated that there is no structural bias or substantial lack of fit in the final model. It is noted that the applicant ran the analyses after excluding potential outliers as defined by Observations with |WRES|>6, |CWRES|>6 or |IWRES|>6. The influence of these outliers was

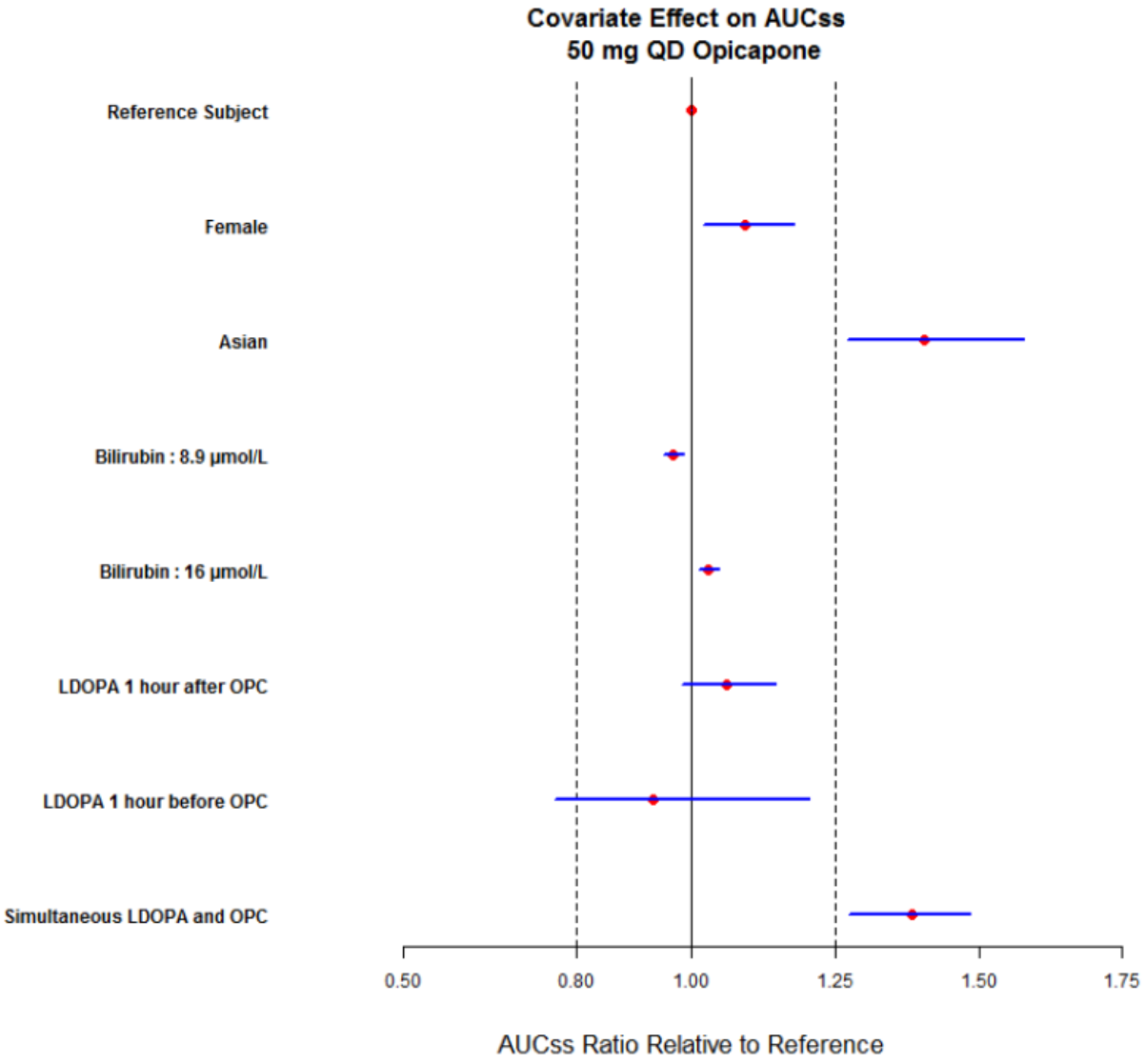
evaluated by comparing estimates of the key model parameters from model fits on data with and without the outliers[43]. Based on differences of approximately 1% in model parameter estimates, the outliers were not considered influential, and therefore were included in full model development. In addition, this reviewer confirmed that the outliers are just random data points and doesn't represent outlying individuals.

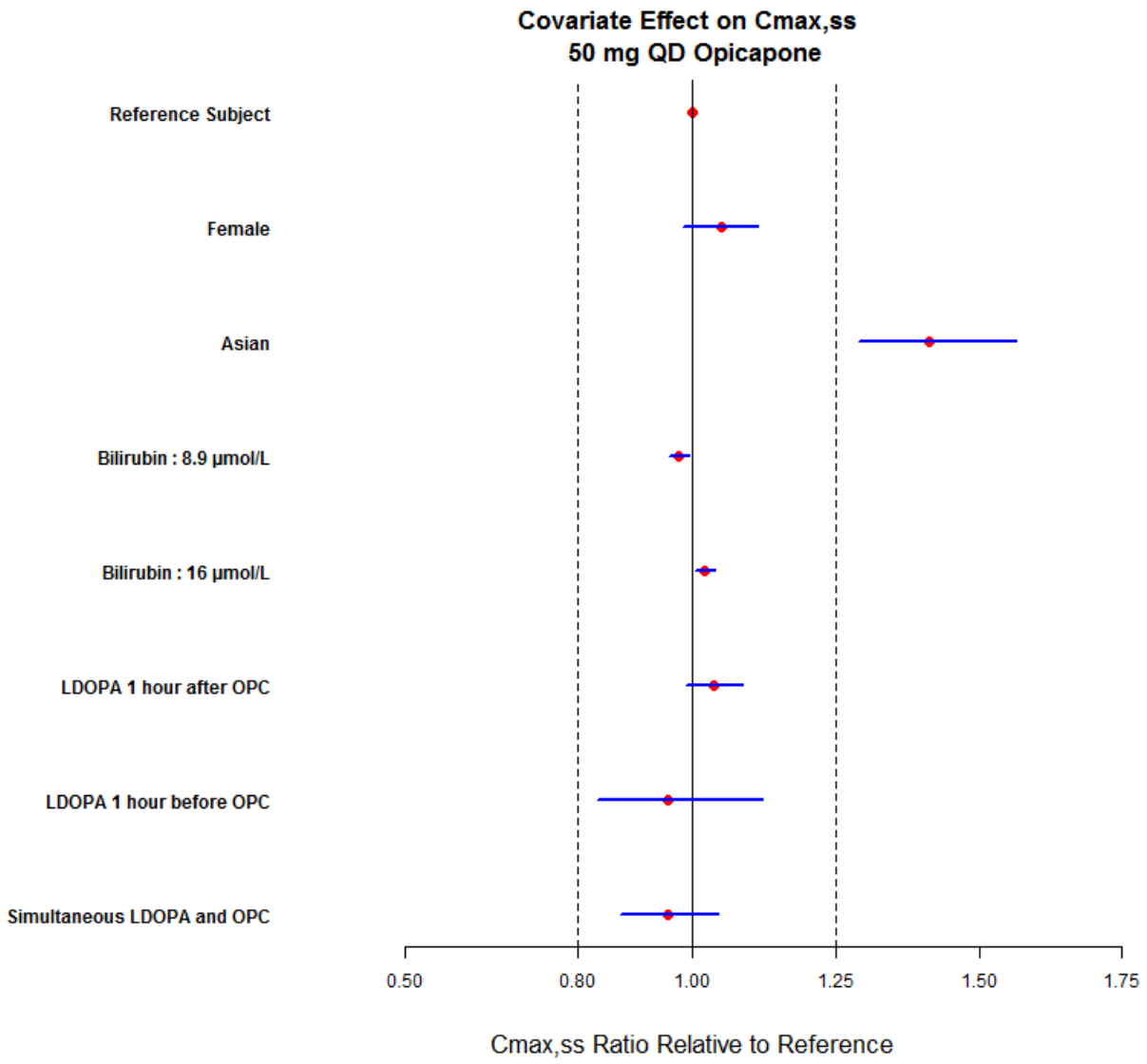
Covariate Effects:

The influence of the key covariates on predicted OPC steady state AUCss and $C_{max,ss}$ is presented in Figure 14 and Figure 15 below.

[43] Per the current FDA guidance for population pharmacokinetics guidance for industry: "the sponsor should investigate the influence of the outliers on the final parameter estimates by refitting the final model to the complete dataset"

Figure 14: Influence of Key Covariates on Predicted OPC Steady State AUCss and C_{max}





Source: 2018-CP-198 report, page 11, Figure S1.

Red circles show the median ratio of the typical parameter value under the test condition compared to the reference conditions. The blue line segments represent the corresponding 90% confidence interval. Vertical dashed lines indicate the interval between ratios of 0.8 to 1.25.

Reference conditions in the simulation included: male, White, healthy subject, body weight = 71 kg, age = 35 years, CLcr = 110.1 mL/min, AST = 22 IU/L, albumin = 45 g/L, total bilirubin = 12 µmol/L, micronized 50 mg OPC qd, no co-administration of levodopa/DDCI, evening dosing, fasted.

Test conditions for total bilirubin represent the 25th and 75th percentiles for subjects in the analysis dataset.

AUCss = steady state area under the plasma drug concentration-time curve over the 24-hour dosing interval; $C_{max,ss}$=steady state maximum plasma drug concentration; OPC = opicapone; qd = once daily; LDOPA = Levodopa/DDCI (levodopa/carbidopa or levodopa/benserazide)

Reviewer Comments:

- *The population PK model identified the following statistically significant covariates: female gender, Asian race and baseline total bilirubin on CL/F; Asian race on V2/F; evening dosing on Ka; and simultaneous levodopa/DDCI co-administration on Ka and F1. Black race was not a significant covariate. Weight was not found to have a significant impact on V1/F or CL/F.*
- *Effects of gender was minimal. Therefore, no dose adjustment is required based on gender.*
- *Model based simulations showed that Asian subjects were predicted to have exposure outside the 80%-125% boundaries [~ 40% higher exposure (AUCss and $C_{max,ss}$) vs. White subjects]. Study BIA-91067-126, a dedicated study in Japanese vs matched Caucasian, showed that AUCss and $C_{max,ss}$ has approximately 20% higher exposure and the upper limit of the 90% CI was outside the 125% boundary (i.e. 152%). Nonetheless, no dose adjustment is required based on these findings.*
- *Renal function (as measured by creatinine clearance) did not affect OPC clearance. However only subjects with normal, mild (n=43) and moderate (n=53) renal impairment were enrolled in phase III studies. This finding was expected given that renal elimination is not a major route for OPC clearance. The effect of severe renal impairment or ESRD patients was not evaluated.*
- *Simultaneous administration of levodopa/DDCI was predicted to result in 38% higher OPC AUCss, without impacting OPC $C_{max,ss}$. Administration of levodopa/DDCI 1 hour before or after OPC was not predicted to affect peak or overall OPC exposure. This result is somewhat different than what was observed in the Phase I study BIA-91067-117. The geometric mean ratios for OPC 50 mg when administered simultaneously with levodopa/carbidopa relative to OPC 50 mg alone (90% confidence interval) for C_{max} and AUC_{inf} were 100 (84-118) and 104.18 (86.56-125.37), respectively. The geometric mean ratios for OPC 50 mg when administered 1 hour before levodopa/carbidopa relative to OPC 50 mg alone (90% confidence interval) for C_{max} and AUC_{inf} were 90.79 (77-107) and 104.74 (88-124), respectively. Nonetheless, it can still be concluded that no OPC dose adjustment is required when simultaneously administered with levodopa/carbidopa.*

Conclusions and reviewer comments

- A population PK model including one-compartment disposition, transit compartment absorption, first order elimination and dose-dependent relative bioavailability adequately described the concentration-time profile of OPC in healthy subjects and patients with Parkinson's disease. This is in alignment with the less than dose proportional finding from the Phase 1 studies.

- In alignment of the dedicated relative bioavailability study (BIA-91067-120), the Pop-PK model estimated that at a dose of 50 mg, micronized OPC has a 67% higher relative bioavailability than nonmicronized OPC.
- The model also predicted that OPC absorption is slower when administered in the evening compared to non-evening dosing. This could be due to the food effect which was not included in the model.
- Race, weight and sex has no or minimal effect on OPC exposure.
- Renal function (as measured by creatinine clearance) did not affect OPC clearance. However only subjects with normal, mild (n=43) and moderate (n=53) renal impairment were enrolled in phase III studies. The effect of severe renal impairment or ESRD patients was not evaluated.

4.3 Summary of Individual Clinical Pharmacology and Efficacy Studies

The OPC clinical development program comprises 38 studies: 34 Phase 1 studies, 2 Phase 2 studies, and 2 Phase 3 studies (double-blind with open-label extension). All Phase 1 studies were conducted in healthy subjects with the exception of 2 Phase 1 studies that included subjects with mild or moderate hepatic impairment in addition to healthy matched control subjects with normal hepatic function (Studies NBI-OPC-1705 and BIA-91067-106) and a PK and pharmacodynamics study in subjects with PD (NBI-OPC-1706). Subjects with PD were enrolled in all Phase 2 and 3 studies.

All of the Phase 1 and 2 studies assessed the PK of OPC and many also assessed the PK of OPC metabolites, including the major circulating metabolite, BIA 9-1103, which is inactive. The PK of OPC was not assessed in the 2 Phase 3 studies due to the fact that OPC was taken at night before bed, and it was considered that the t½ of OPC was not long enough to permit quantitation of OPC at post-dose clinic visits the following day. Most Phase 1 and 2 studies also investigated the pharmacodynamics of OPC, namely the inhibition of S-COMT. Table 10 provides an overview of the clinical studies contributing to the clinical pharmacology and clinical efficacy of OPC.

Notably, three human mass balance and metabolite identification studies have been conducted with OPC. The third study (BIA-91067-130) is considered the definitive mass balance and metabolite identification study and the initial 2 studies (BIA-91067-103 and BIA-91067-122) are considered supportive and to be in general agreement with the definitive study.

Table 10: Overview of Clinical Development Program

Study Number	Key Objectives
Phase **1 Studies**	
Absorption, **Distribution, Metabolism, and Excretion (ADME)**	
BIA-91067-103	**Assess the ADME of ^{14}C-OPC (100 mg single dose)**
BIA-91067-122	**Assess the ADME of ^{14}C-OPC (100 mg single dose)**
BIA-91067-130	**Assess the ADME of ^{14}C-OPC (100 mg single dose)**
Pharmacokinetics **and Pharmacodynamics**	
BIA-91067-101[a]	**Characterize the PK and pharmacodynamics of single dose OPC**
BIA-91067-102[a]	**Characterize the PK and pharmacodynamics of multiple dose OPC**
BIA-91067-107[a]	**Effect of concomitant single dose IR levodopa/benserazide and single dose OPC**
BIA-91067-108[a]	**Effect of concomitant single dose IR levodopa/carbidopa and single dose OPC**
BIA-91067-109[a]	**Effect of concomitant single dose CR levodopa/benserazide and single dose OPC**
BIA-91067-110[a]	**Effect of concomitant single dose CR levodopa/carbidopa and single dose OPC**

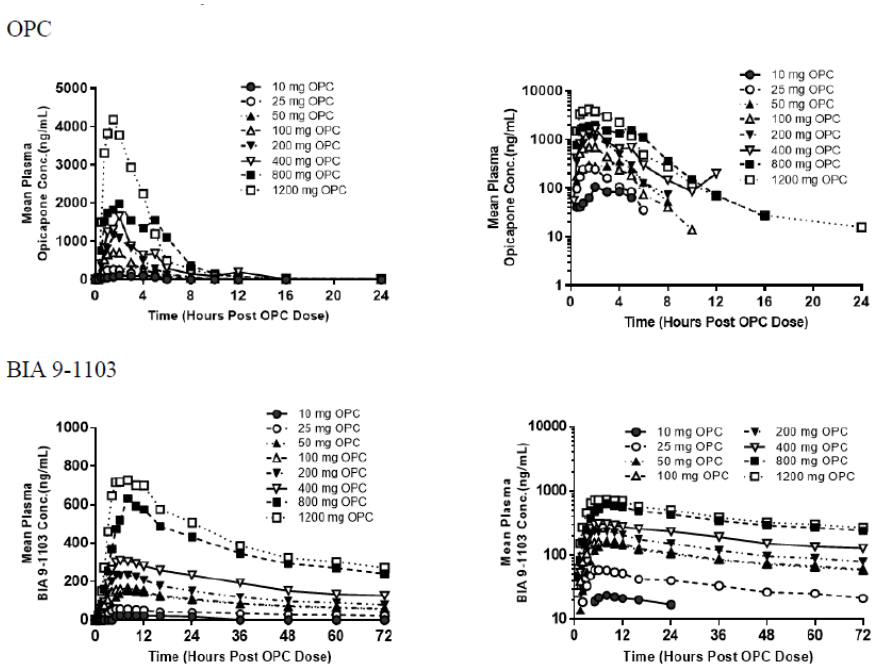
BIA-91067-117[a]	**Effect of concomitant and separated (1 hour) single dose IR levodopa/carbidopa and single dose OPC**
BIA-91067-114[a]	**Effect of separated (1 hour) single dose IR levodopa/carbidopa with multiple dose OPC or entacapone**
BIA-91067-118[a]	**Effect of separated (1 hour) single dose IR levodopa/DDCI with multiple dose OPC**
BIA-91067-123[a]	**Effect of separated (12 hour) single dose IR levodopa/DDCI with multiple dose OPC**
BIA-91067-124[b]	**Effect of separated (10 hours) multiple dose IR levodopa/carbidopa and multiple dose OPC compared to concomitant levodopa/carbidopa and entacapone**
BIA-91067-111[a]	**Effect of OPC on cardiac repolarization**
Intrinsic **Factors**	
BIA-91067-105[a]	**Effect of age**
NBI-OPC-1705[b]	**Effect of mild hepatic impairment**
BIA-91067-106[a]	**Effect of moderate hepatic impairment**
BIA-91067-126[b]	**Effect of ethnicity (Japanese vs Caucasian)**
Extrinsic **Factors**	
BIA-91067-112[a]	**Effect of single dose OPC on single dose rasagiline (selective MAO-B inhibitor)**
BIA-91067-113[a]	**Effect of single dose rasagiline (selective MAO-B inhibitor) on single dose OPC**
BIA-91067-115[a]	**Effect of single dose OPC on single dose repaglinide (CYP2C8 substrate)**
NBI-OPC-1708[b]	**Effect of multiple dose OPC on single dose repaglinide (CYP2C8 substrate)**
BIA-91067-116[a]	**Effect of single dose OPC on single dose warfarin (CYP2C9 substrate)**
BIA-91067-127[b]	**Effect of multiple dose OPC on single dose warfarin (CYP2C9 substrate)**
BIA-91067-125[b]	**Effect of acetaminophen (inorganic sulfate depleter) on single dose OPC**
NBI-OPC-1707[b]	**Effect of quinidine (MDR1 inhibitor) on OPC**
Phase **1 and 2 Studies in Subjects with Parkinson's Disease**	
NBI-OPC-1706[b]	**Patient PK and pharmacodynamics**
BIA-91067-201[a]	**Single dose OPC co-administered with single dose IR levodopa/DDCI**
BIA-91067-202[a]	**Multiple dose OPC and multiple dose IR levodopa/DDCI (1 hour apart)**
Phase **3 Studies in Subjects with Parkinson's Disease**	
BIA-91067-301[b]	**Multiple dose OPC co-administered with levodopa/DDCI**
BIA-91067-302[b]	**Multiple dose OPC co-administered with levodopa/DDCI**

ADME = absorption, distribution, metabolism, and excretion; CR = controlled release; CYP = cytochrome P450; DDCI = dopa decarboxylase inhibitor; IR = immediate release; MAO = monoamine oxidase; MDR1 = multidrug resistance protein 1; PK = pharmacokinetic(s); qd = once daily. [a] Nonmicronized formulation. [b] Micronized formulation.

4.4 Clinical Pharmacokinetics/Pharmacodynamic

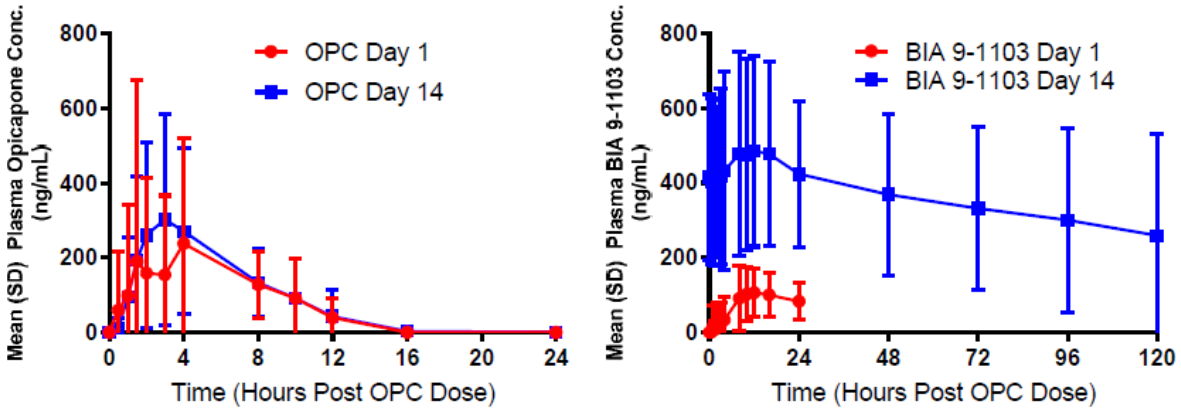
4.4.1. PK Profiles of OPC and BIA-9-1103 from Selected Studies.

Figure 15: Mean Plasma Concentration-Time Profiles of OPC and BIA 9-1103 Following Single Doses of 10 to 1200 mg Nonmicronized OPC (Study BIA-91067-101)



Source: Study BIA-91067-101 adapted from Figures 5, 6, and 12.

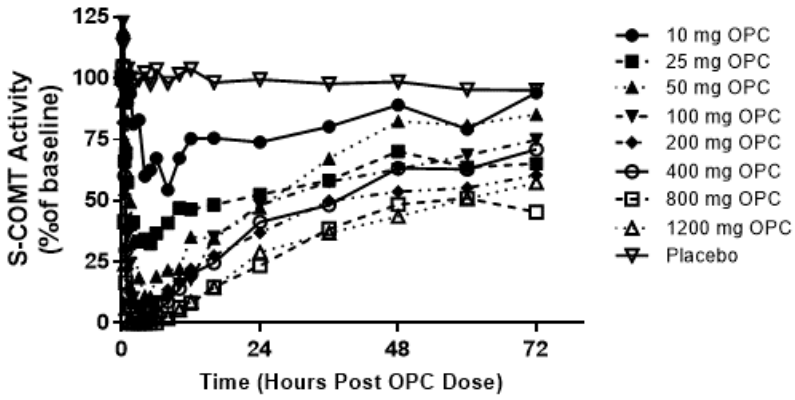
Figure 16 Mean (SD) Plasma Concentration-Time Profiles of OPC and BIA 9-1103 Following Single (Day 1) and Multiple (Day 14) Doses of 50 mg qd Micronized OPC (Study NBI-OPC-1706)



Source: Summary of Clinical Pharmacology; page 82, Figure 9; adapted from Study NBI-OPC-1706 Figure 2.

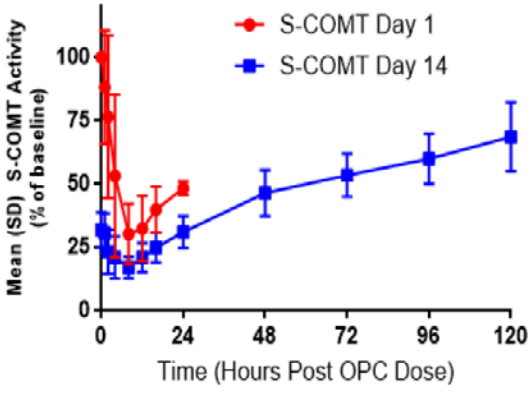
4.4.2. S-COMT Profiles from Selected Studies.

Figure 17: Mean S-COMT Inhibition-Time Profiles After Single Doses (Day 1) of 10 to 1200 mg Nonmicronized OPC or Placebo (Study BIA-91067-101)

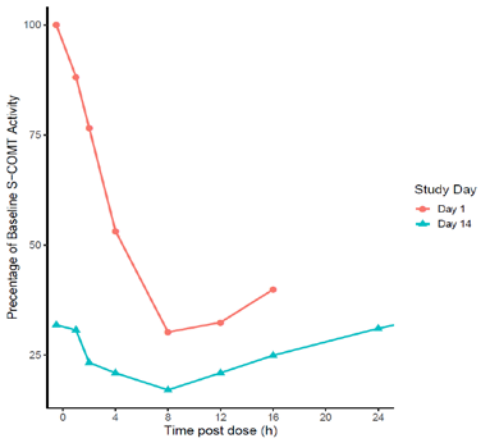


Source: Study BIA-91067-101 Figure 1.

Figure 18: Mean (SD) Percent Change from Baseline in S-COMT Inhibition Following Single (Day 1) and Multiple (Day 14) Doses of 50 mg qd Micronized OPC (Study NBI-OPC-1706)



Source: Summary of Clinical Pharmacology; page 85, Figure 11; adapted from Study NBI-OPC-1706 Figure 8.



Source: Figure created by the reviewer to focus on the first 24 hours.

4.4.3. Effect of OPC Concomitant Administration on Levodopa PK from Selected Studies: Co-Administration versus Various Staggered Administration.

The effect of simultaneous and staggered administration of OPC with LD/carbidopa was evaluated in various Phase 1 studies (Table 11)[44]. The geometric mean ratios of levodopa and its main metabolite 3-OMD are summarized in Table 12-Table 18. In general, these studies demonstrated dose dependent increase in levodopa exposure and dose dependent reduction in 3-OMD exposure. No conclusion can be made regarding the effect of simultaneous versus staggered dosing of OPC with levodopa/carbidopa dosing as the effect on LD peak concentration is not consistent across these studies. For example, Study BIA-91067-117 evaluated the effect of single-dose OPC and single-dose immediate release levodopa/carbidopa administered simultaneously or 1 hour apart. Results of this study indicated that levodopa peak concentration was similar when administered simultaneously versus 1 hour apart from OPC. Notably, in Phase 3 studies, the protocol specified administering OPC dose at bedtime at least 1 hour after the last daily dose of levodopa/DDCI.

Table 11: Summary of Clinical Studies that Evaluated the Effect of Concomitant Administration of OPC on Levodopa PK

Study Number	Objectives	Study Design	Treatment Regimen
BIA-91067-108[a]	Effect of concomitant single dose IR levodopa/carbidopa and single dose OPC	Single-center, randomized, double-blind, PBO-controlled, 4-period crossover, single-dose, PK-PD interaction study with OPC and levodopa/carbidopa	**Single doses of PBO or nonmicronized OPC API (25 mg, 50 mg, or 100 mg) in each period concomitantly with 100/25 mg immediate-release levodopa/carbidopa**
BIA-91067-110[a]	Effect of concomitant single dose CR levodopa/carbidopa and single dose OPC	Single-center, randomized, double-blind, PBO-controlled, 4-period crossover, single-dose, PK-PD interaction study with OPC and levodopa/carbidopa	**Single doses of PBO or nonmicronized OPC API (25 mg, 50 mg, or 100 mg) in each period concomitantly with 100/25 mg controlled-release levodopa/carbidopa**
BIA-91067-117[a]	Effect of concomitant and separated (1 hour)	Single-center, randomized, open-label,	**Single doses of 50 mg nonmicronized OPC API**

[44] The applicant also evaluated the effect of concomitant administration of OPC with LD/Benserazide in Studies: BIA-91067-107 and BIA-91067-109. However, because benserazide is not approved in US, these studies were not part of the review.

	single dose IR levodopa/carbidopa and single dose OPC	4-period crossover, single-dose, PK study with levodopa/carbidopa	**alone, or concomitantly with 100/25 mg levodopa/carbidopa immediate-release, or 1 hour before the 100/25 mg immediate-release levodopa/carbidopa dose, or 100/25 mg immediate-release levodopa/carbidopa alone per study period**
BIA-91067-114[a]	Effect of separated (1 hour) single dose IR levodopa/carbidopa with multiple dose OPC or entacapone	Single-center, randomized, double-blind, PBO- and active-controlled, parallel-group, multiple-dose study to investigate the effect of OPC on levodopa PK compared to PBO and ENT	**Days 1-7:** **Group 1 received PBO at all dosing times** **Groups 2-4 received nonmicronized OPC API (5 mg, 15 mg, or 30 mg) as the first dose of each day and PBO at the other 3 daily dosing times** **Group 5 received PBO as the first dose of each day and 200 mg ENT at the other 3 daily dosing times**
BIA-91067-118[a]	Effect of separated (1 hour) single dose IR levodopa/DDCI with multiple dose OPC	Single-center, randomized, double-blind, PBO-controlled, multiple-dose study to investigate levodopa PK in steady-state conditions with levodopa/carbidopa and levodopa/benserazide	**PBO or nonmicronized OPC API (5 mg, 15 mg, or 30 mg) qd for 28 days, concomitantly with 100/25 mg immediate-release levodopa/carbidopa on Day 21 and 100/25 mg immediate-release levodopa/benserazide on Day 28**
BIA-91067-123[a]	Effect of separated (12 hour) single dose IR	Single-center, randomized, double-blind, PBO-controlled,	**PBO or nonmicronized OPC API (5 mg, 15 mg, or 50 mg) qd for 18**

	levodopa/DDCI with multiple dose OPC	multiple-dose study to investigate levodopa PK in steady-state conditions with levodopa/carbidopa and levodopa/benserazide	**days, with 100/25 mg levodopa/carbidopa on Day 11 and 100/25 mg levodopa/benserazide on Day 18 after the OPC/PBO dose**
BIA-91067-124[b]	Effect of separated (10 hours) multiple dose IR levodopa/carbidopa and multiple dose OPC compared to concomitant levodopa/carbidopa and entacapone	Single-center, randomized, double-blind, gender-balanced, placebo-controlled study in 4 groups of 20 healthy subjects each (10 male and 10 female).	**Group 1 PBO for 12 days or PBO for 11 days and ENT 200 mg administered concomitantly with levodopa/carbidopa on Day 12 Group 2-4 PBO or micronized OPC API (25, 50, 75 mg) qd for 11 days, concomitantly with 100/25 mg levodopa/carbidopa on Day 12**
BIA-91067-201[a]	Effect of single-dose OPC on levodopa PK, COMT activity, and motor response in PD patients treated with levodopa/DDCI	Three-center, randomized, double-blind, placebo-controlled, 4-way crossover, single dose study	**Four separate treatment period where each subject received doses of 25, 50, 100 mg OPC or placebo co-administered with LEVODOPA/DDCI according to the following: Day 1: Admission (no drug administered). Day 2: 100/25 mg levodopa/DDCI single dose administered**

			following an overnight fast of 8 hours. **Day 3: 25, 50, or 100 mg OPC or placebo single dose co-administered simultaneously with 100/25 mg levodopa/DDCI single dose. Administration followed an overnight fast of 8 hours.** **Day 4: 100/25 mg levodopa/DDCI single dose administered following an overnight fast of 8 hours.**
BIA-91067-202[a]	**Effect of multiple-dose OPC on levodopa PK, COMT activity, and motor response in PD patients treated with levodopa/DDCI**	**Multicenter, randomized, double-blind, placebo-double-blind, placebo-**	**Nonmicronized OPC API (5, 15, or 30 mg) or placebo qd for 21 to 28 days, 1 hour prior to morning levodopa/DDCI dose**

Source: Table created by the reviewer. [a]Nonmicronized formulation. [b]Micronized formulation.
DDCI = decarboxylase inhibitor (carbidopa or benserazide).

Table 12: Summary of Statistical Analysis of Levodopa and 3-OMD Pharmacokinetics Following Single Doses of 25 to 100 mg Nonmicronized OPC/Placebo Co-administered Simultaneously with 100/25 mg Levodopa/Carbidopa (Study BIA-91067-108)

Parameter	OPC/Placebo Geometric Mean Ratio % (90% Confidence Interval)		
	25 mg OPC	50 mg OPC	100 mg OPC
Levodopa			
C_{max}	103.75 (91.04; 118.23)	128.46 (112.83; 146.25)	118.14 (103.67; 134.63)
$AUC_{0\text{-}tlast}$	103.35 (93.55; 114.17)	109.29 (98.99; 120.64)	115.70 (104.73; 127.82)
$AUC_{0\text{-}\infty}$	103.13 (94.02; 113.12)	109.85 (100.22; 120.41)	116.64 (106.34; 127.94)
3-OMD			
C_{max}	94.06 (85.11; 103.95)	85.42 (77.35; 94.33)	82.06 (74.26; 90.69)
$AUC_{0\text{-}tlast}$	92.04 (79.53; 106.52)	75.09 (64.94; 86.82)	68.15 (58.89; 78.87)
$AUC_{0\text{-}\infty}$	93.59 (83.66; 104.71)	79.57 (71.18; 88.95)	72.60 (64.89; 81.22)

Source: Study BIA-91067-108 Table E and Table G. AUC0-tlast = area under the concentration-time curve from time 0 to the last measurable timepoint; AUC0-∞ = area under the concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration; 3-OMD = 3-O-methyldopa; OPC = opicapone.

Table 13: Summary of Statistical Analysis of Levodopa and 3-OMD Pharmacokinetics Following Single Doses of 25 to 100 mg Nonmicronized OPC/Placebo Co-administered Simultaneously with 100/25 mg Levodopa/Carbidopa (Study BIA-91067-110)

Parameter	OPC/Placebo Geometric Mean Ratio % (90% Confidence Interval)		
	25 mg OPC	50 mg OPC	100 mg OPC
Levodopa			
C_{max}	134.33 (113.78; 158.58)	120.58 (101.61; 143.09)	108.09 (91.56; 127.61)
$AUC_{0-tlast}$	124.64 (107.74; 144.19)	130.43 (112.26; 151.55)	136.80 (118.25; 158.26)
$AUC_{0-\infty}$	123.29 (106.88; 142.21)	130.99 (113.08; 151.74)	138.14 (119.76; 159.34)
3-OMD			
C_{max}	96.02 (86.23; 106.91)	75.29 (67.39; 84.12)	63.65 (57.16; 70.87)
$AUC_{0-tlast}$	92.42 (78.81; 108.39)	69.94 (59.33; 82.44)	56.02 (47.76; 65.69)
$AUC_{0-\infty}$	93.88 (84.00; 104.92)	75.59 (67.38; 84.77)	63.43 (56.76; 70.89)

Source: Study BIA-91067-110 Table E and Table G.

AUC0-tlast = area under the concentration-time curve from time 0 to the last measurable timepoint; AUC0-∞ = area under the concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration; 3-OMD = 3-O-methyldopa; OPC = opicapone.

Table 14: Summary of Statistical Analysis of Pharmacokinetics of Levodopa and 3-OMD Following Single Doses of 50 mg Nonmicronized OPC Either Co-administered Simultaneously with or Administered 1 Hour Before 100/25 mg Levodopa/Carbidopa (Study BIA-91067-117)

Parameter	Geometric Mean Ratio % (90% Confidence Interval)		
	OPC with Simultaneous L/C vs L/C Alone	OPC 1 Hour Before L/C vs L/C Alone	OPC 1 Hour Before L/C vs OPC Simultaneous with L/C
Levodopa			
C_{max}	112.10 (96.94; 129.64)	102.96 (89.36; 118.62)	91.84 (79.51; 106.09)
$AUC_{0-tlast}$	104.23 (96.88; 112.14)	114.56 (106.65; 123.05)	109.91 (102.17; 118.24)
$AUC_{0-\infty}$	103.13 (94.02; 113.12)	109.85 (100.22; 120.41)	108.51 (101.24; 116.31)
3-OMD			
C_{max}	79.81 (76.21; 83.57)	68.83 (65.80; 72.01)	86.25 (82.37; 90.31)
$AUC_{0-tlast}$	76.72 (71.66; 82.13)	66.43 (62.15; 71.02)	86.60 (80.89; 92.70)
$AUC_{0-\infty}$	78.39 (73.08; 84.09)	68.26 (63.73; 73.11)	87.07 (81.18; 94.74)

Source: Study BIA-91067-117 Table E and Table G.

AUC0-tlast = area under the concentration-time curve from time 0 to the last measurable timepoint; AUC0-∞ = area under the concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration; L/C = levodopa/carbidopa; 3-OMD = 3-O-methyldopa; OPC = opicapone.

Table 15: Pharmacokinetics of Levodopa Following Multiple Doses of Nonmicronized OPC, Entacapone, or Placebo Administered 1 Hour Before a Single Dose of 100/25 mg Levodopa/Carbidopa (Study BIA-91067-114)

Parameter[a]	Placebo	OPC 5 mg qd	OPC 15 mg qd	OPC 30 mg qd	Entacapone 200 mg tid
N	16	16	16	16	16
t_{max}, h	0.75 (0.25-1.0)	0.75 (0.25-1.0)	0.75 (0.25-3.0)	0.75 (0.25-1.0)	0.75 (0.5-2.0)
C_{max}, ng/mL	1076 (27.2)	1106 (38.0)	943 (34.5)	981 (49.8)	928 (26.4)
$AUC_{0\text{-tlast}}$, ng×h/mL	1578 (20.3)	1785 (32.2)	2102 (27.1)	2202 (27.5)	2146 (25.1)
$AUC_{0\text{-}\infty}$, ng×h/mL	1649 (19.0)	1873 (30.5)	2233 (25.9)	2381 (26.2)	2253 (24.0)
$t_{½}$, h	1.36 (21.6)	1.55 (20.6)	1.96 (19.0)	2.20 (16.1)	1.67(16.7)
	OPC/Placebo Geometric Mean Ratio % (90% Confidence Interval)				
C_{max}	-	98.84 (78.61; 124.28)	85.92 (68.33; 108.03)	84.64 (67.31; 106.43)	-
$AUC_{0\text{-tlast}}$	-	110.16 (93.90; 129.23)	131.17 (111.81; 153.88)	137.56 (117.26; 161.38)	-
$AUC_{0\text{-}\infty}$	-	110.94 (95.36; 129.08)	133.49 (114.73; 155.31)	142.51 (122.49; 165.81)	-
	OPC/Entacapone Geometric Mean Ratio % (90% Confidence Interval)				
C_{max}	-	114.85 (91.12; 144.76)	99.84 (79.21; 125.83)	98.35 (78.03; 123.97)	-
$AUC_{0\text{-tlast}}$	-	81.71 (69.33; 96.29)	97.29 (82.55; 114.66)	102.03 (86.57; 120.24)	-
$AUC_{0\text{-}\infty}$	-	81.89 (70.04; 95.74)	98.53 (84.27; 115.19)	105.19 (89.87; 122.98)	-

Source: Study BIA-91067-114 Table D and Table E.

AUC0-tlast = area under the concentration-time curve from time 0 to the last measurable timepoint; AUC0-∞ = area under the concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration; CV% = percent coefficient of variation; N = maximum number of subjects with data; OPC = opicapone; qd = once daily; t½ = elimination half-life; T_{max} = time to maximum observed plasma concentration; tid = 3 times a day.

[a]Values are arithmetic mean (CV%) except for T_{max} which is median (minimum-maximum).

Table 16: Summary of Statistical Analysis of Levodopa Pharmacokinetics Following Multiple Doses of Nonmicronized OPC or Placebo Administered 1 Hour Before a Single Dose of 100/25 mg Levodopa/Carbidopa (Study BIA-91067-118)

Parameter	OPC/Placebo Geometric Mean Ratio % (90% Confidence Interval)		
	5 mg qd OPC	15 mg qd OPC	30 mg qd OPC
OPC + Levodopa/Carbidopa versus Placebo + Levodopa/Carbidopa (Day 21)			
C_{max}	122.97 (97.63; 154.89)	115.44 (91.65; 145.40)	90.06 (76.26; 120.99)
$AUC_{0\text{-tlast}}$	178.08 (139.55; 227.24)	160.51 (125.78; 204.82)	149.02 (116.78; 190.16)
$AUC_{0\text{-}\infty}$	177.12 (141.23; 222.12)	161.71 (128.95; 202.80)	150.07 (119.67; 188.21)

Source: Study BIA-91067-118 Table E.

AUC0-tlast = area under the concentration-time curve from time 0 to the last measurable timepoint; AUC0-∞ = area under the concentration-time curve extrapolated to infinity; Cmax = maximum observed plasma concentration; OPC = opicapone; qd = once daily.

Table 17: Summary of Statistical Analysis of Levodopa Pharmacokinetics Following 100/25 mg Levodopa/Carbidopa Administered at least 10 Hours After Multiple Doses of Micronized OPC or Placebo (Days 1 to 11), or Concomitantly with Entacapone or Placebo (Day 12) (Study BIA-91067-124)

Parameter	OPC 25 mg qd	OPC 50 mg qd	OPC 75 mg qd	Entacapone 200 mg tid
First Dose of Levodopa/Carbidopa				
	OPC/Placebo or Entacapone/Placebo Geometric Mean Ratio % (90% Confidence Interval)			
C_{max}	113.81 (87.05; 148.78)	96.01 (73.76; 124.97)	101.76 (78.18; 132.45)	76.60 (58.85; 99.71)
AUC_{0-5}	129.29 (95.52; 175.00)	117.71 (87.39; 158.54)	139.10 (103.27; 187.34)	86.13 (63.94; 116.00)
	OPC/Entacapone Geometric Mean Ratio % (90% Confidence Interval)			
C_{max}	148.57 (111.93; 197.20)	125.34 (94.86; 165.60)	132.84 (100.54; 175.51)	NA
AUC_{0-5}	150.12 (107.37; 209.90)	136.67 (98.28; 190.05)	161.50 (116.14; 224.59)	NA
Second Dose of Levodopa/Carbidopa				
	OPC/Placebo or Entacapone/Placebo Geometric Mean Ratio % (90% Confidence Interval)			
C_{max}	98.16 (70.28; 137.11)	123.95 (89.23; 172.18)	132.03 (95.04; 183.41)	80.85 (58.20; 112.31)
AUC_{0-5}	120.64 (87.91; 165.54)	146.29 (107.16; 199.72)	162.60 (119.11; 221.99)	102.69 (75.22; 140.19)
	OPC/ Entacapone Geometric Mean Ratio % (90% Confidence Interval)			
C_{max}	121.41 (84.53; 174.39)	153.30 (107.36; 218.91)	163.30 (114.36; 233.18)	NA
AUC_{0-5}	117.48 (82.50; 167.28)	142.46 (100.62; 201.70)	158.35 (111.84; 224.19)	NA
Third Dose of Levodopa/Carbidopa				
	OPC/Placebo or Entacapone/Placebo Geometric Mean Ratio % (90% Confidence Interval)			
C_{max}	97.45 (67.76; 140.14)	110.96 (77.61; 158.64)	136.17 (95.24; 194.67)	92.33 (64.58; 131.99)
AUC_{0-5}	114.36 (78.00; 167.68)	142.07 (97.50; 207.01)	176.30 (120.99; 256.88)	107.57 (73.83; 156.74)
$AUC_{0-tlast}$	132.79 (86.45; 203.96)	176.22 (115.53; 268.79)	216.06 (141.65; 329.56)	113.69 (74.53; 173.41)
AUC_{0-24}	141.42 (104.08; 192.14)	152.62 (112.89; 206.34)	178.90 (132.32; 241.86)	102.97 (76.16; 139.21)
	OPC/ Entacapone Geometric Mean Ratio % (90% Confidence Interval)			
C_{max}	105.55 (71.50; 155.80)	120.18 (81.94; 176.28)	147.49 (100.55; 216.33)	NA
AUC_{0-5}	106.31 (69.45; 162.75)	132.07 (86.88; 200.78)	163.89 (107.80; 249.15)	NA
$AUC_{0-tlast}$	116.80 (72.26; 188.79)	155.00 (96.55; 248.59)	190.04 (118.50; 304.79)	NA
AUC_{0-24}[a]	137.34 (97.56; 193.34)	148.23 (105.88; 207.50)	173.74 (124.11; 243.22)	NA

Source: Study BIA-91067-124 Table 11.4.2-5, Table 11.4.2-6, Table 11.4.2-7, and Table 11.4.2-8.

AUC0-5/24 = area under the concentration-time curve from time 0 to 5/24 hours; AUC0-tlast = area under the concentration-time curve from time 0 to the last measurable timepoint; C_{max} = maximum observed plasma concentration; NA = not applicable; OPC = opicapone; qd = once daily; tid = 3 times a day.

[a]AUC0-24 is the sum of AUC0-5 from the first and second doses and AUC0-tlast from the third dose.

Table 18: Summary of Statistical Analysis of Levodopa Pharmacokinetics Following Multiple Doses of Nonmicronized OPC or Placebo Administered 12 Hours Before a Single Dose of 100/25 mg Levodopa/DDCI (Study BIA-91067-123)

Parameter	OPC/Placebo Geometric Mean Ratio % (90% Confidence Interval)		
	5 mg qd OPC	15 mg qd OPC	50 mg qd OPC
OPC/Placebo + Levodopa/Carbidopa (Day 11)			
C_{max}	103 (85; 125)	113 (94; 135)	106 (90; 126)
$AUC_{0\text{-tlast}}$	124 (106; 144)	143 (122; 168)	165 (139; 195)
$AUC_{0\text{-}\infty}$	125 (108; 145)	146 (126; 170)	170 (144; 199)
OPC/Placebo + Levodopa/Benserazide (Day 18)			
C_{max}	78 (60; 101)	127 (103; 157)	102 (78; 132)
$AUC_{0\text{-tlast}}$	114 (98; 134)	160 (139; 184)	165 (136; 201)
$AUC_{0\text{-}\infty}$	115 (98; 134)	160 (140; 184)	166 (137; 201)

Source: Study BIA-91067-123 Table 8 and Table 10.

AUC0-tlast = area under the concentration-time curve from time 0 to the last measurable timepoint; AUC0-∞ = area under the concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration; DDCI = dopa decarboxylase inhibitor; OPC = opicapone; qd = once daily.

Table 19: Summary of Statistical Analysis of Levodopa Pharmacokinetic Parameters Following Simultaneous Administration of Levodopa/DDCI with and Without Single Doses of OPC/Placebo (Study BIA-91067-201)

Levodopa Parameter	Geometric Mean Ratio % (90% Confidence Interval)			
		OPC Dose (Nonmicronized)		
	Placebo	25 mg	50 mg	100 mg
Levodopa/DDCI + OPC (Day 3) versus Levodopa/DDCI + Placebo (Day 3)				
C_{max}	-	91.43 (74.78, 111.80)	108.26 (88.45, 132.52)	129.05 (105.71, 157.53)
$AUC_{0\text{-}6}$	-	103.74 (83.30, 129.20)	116.41 (93.36, 145.14)	134.83 (108.46, 167.62)
Levodopa/DDCI +OPC/Placebo (Day 3) versus Levodopa/DDCI Alone (Day 2)				
C_{max}	93.49 (62.23, 140.45)	90.10 (60.66, 133.84)	117.00 (78.87, 173.56)	144.54 (104.41, 200.09)
$AUC_{0\text{-}6}$	82.11 (55.90, 120.61)	100.68 (66.58, 152.24)	121.94 (88.57, 167.89)	133.18 (90.22, 196.60)
Levodopa/DDCI Alone (Day 4) versus Levodopa/DDCI + Alone (Day 2)				
C_{max}	83.26 (55.84, 124.16)	109.18 (80.03, 148.94)	128.79 (87.21, 190.19)	120.93 (79.59, 183.74)
$AUC_{0\text{-}6}$	93.45 (63.99, 136.48)	110.54 (77.14, 158.40)	138.79 (101.18, 190.38)	132.36 (86.56, 202.39)

Source: Study BIA-91067-201 Table E and Table F.

AUC0-6 = area under the concentration-time curve from time 0 to 6 hours; C_{max} = maximum observed plasma concentration; DDCI = dopa decarboxylase inhibitor; OPC = opicapone.

Table 20: Pharmacokinetics of Levodopa and 3-OMD Following Administration of Levodopa/DDCI 1 Hour Before OPC in Subjects Administered Once-Daily Nonmicronized OPC/Placebo (Study BIA-91067-202)

Parameter	Second Levodopa Test /First Levodopa Test Geometric Mean Ratio % (90% Confidence Interval)			
	Placebo	5 mg qd OPC	15 mg qd OPC	30 mg qd OPC
Levodopa				
C_{max}	80.42 (63.33; 102.11)	133.21 (96.99; 182.95)	108.11 (77.78; 150.26)	148.25 (104.38; 210.56)
AUC_{0-6}	88.44 (69.47; 112.59)	124.73 (95.90; 162.24)	153.93 (104.43; 226.89)	165.61 (125.64; 218.29)
3-OMD				
C_{max}	80.03 (51.85; 123.53)	58.22 (46.11; 73.53)	31.03 (19.57; 49.20)	27.82 (19.16; 40.41)
AUC_{0-6}	87.76 (58.52; 131.63)	62.94 (50.29; 78.80)	34.01 (20.28; 57.01)	28.42 (19.63; 41.16)

Source: Study BIA-91067-202 Table G and Table I.

AUC0-6 = area under the concentration-time curve from time 0 to 6 hours; C_{max} = maximum observed plasma concentration; DDCI = dopa decarboxylase inhibitor; 3-OMD = 3-O-methyldopa; OPC = opicapone; qd = once daily.

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