



Pharmacokinetics, Pharmacodynamics, and Tolerability of Opicapone in Healthy Chinese and Caucasian Subjects: An Open-Label, Single-Center, Phase 1 Study

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ABSTRACT

Introduction: This study evaluated the pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple doses of opicapone (OPC) in healthy Chinese and Caucasian subjects.

Methods: In this open-label, single-center, phase 1 study, eligible Chinese subjects received one of three OPC doses (25, 50, or 100 mg), and Caucasian subjects received either 25 or 50 mg

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of OPC. All subjects were administered a single dose of OPC, whereas subjects in the 50-mg OPC group continued to receive once-daily doses of 50 mg OPC for 10 days. The primary endpoint was to evaluate and compare the plasma concentrations and PK parameters of OPC and its main metabolite, and erythrocyte-soluble catechol-O-methyltransferase (S-COMT) activity in Chinese subjects with that of Caucasian subjects. The secondary endpoint was to evaluate the safety of OPC in Chinese subjects. The estimated results for geometric mean ratios (GMRs) were evaluated with the standard bioequivalence (BE) limits between 80% and 125% to evaluate the ethnic differences. All statistical analyses were performed using SAS version 9.4. **Results:** In total, 70 subjects (45 Chinese, 25 Caucasian) were enrolled; the majority of them were male (85.7%). The plasma exposure of both OPC and BIA 9-1103 increased in an approximately dose-proportional manner in both populations. Maximum S-COMT inhibition ranged from 79% to 95% after a single dose and was about 94% after a 10-day once-daily regimen in both populations. The point estimates of GMRs (Chinese/Caucasian) and 90% CI, except C_{max} in 25-mg and 50-mg OPC groups, for PK and PD parameters were within 80% to 125%. Furthermore, no new risks or safety concerns associated with OPC were identified, indicating a tolerable safety profile in healthy Chinese subjects.

Conclusion: Ethnicity had no significant impact on PK and PD parameters after single or multiple doses of OPC, and OPC was safe and tolerable in healthy Chinese subjects.

Trial Registration: ChiCTR number, CTR20192230.

Keywords: Clinical trial; COMT inhibitor; Ethnicity; Opicapone; Pharmacodynamics; Pharmacokinetics; Tolerability

Key Summary Points

Why carry out this study?

The available catechol-*O*-methyltransferase (COMT) inhibitors have clinical limitations. Opicapone (OPC), a novel third-generation COMT inhibitor, was developed to overcome such limitations

We conducted this study to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of OPC when administered as single and multiple doses in healthy Chinese and Caucasian subjects

What was learned from the study?

The plasma exposure of both OPC and BIA 9-1103 increased in an approximately dose-proportional manner in both populations

The point estimates of geometric mean ratios (Chinese/Caucasian) and 90% CI, except C_{\max} in 25-mg and 50-mg OPC groups, for PK and PD parameters were all within 80% to 125%, indicating no significant differences in PK and PD profiles between Chinese and Caucasian subjects. Furthermore, no new risks or safety concerns associated with OPC were identified

INTRODUCTION

For decades, levodopa (L-DOPA) has remained the gold standard in treating Parkinson's disease, a progressive neurodegenerative disease characterized by a deficiency of neurotransmitters, especially dopamine [1–3]. L-DOPA is often used in combination with dopa-decarboxylate inhibitors (DDCIs) to increase its uptake in the brain and reduce side effects [4]. However, only a small proportion of L-DOPA reaches the brain because of the degradation of the drug by the enzyme catechol-*O*-methyltransferase (COMT) [5]. Therefore, adjunctive therapy with peripheral COMT inhibitors is suggested to inhibit the peripheral levodopa metabolism (*O*-methylation of L-DOPA to 3-*O*-methyldopa [3-OMD]) [6, 7]. Multiple guidelines also recommend COMT inhibitors in patients with advanced Parkinson's disease and motor fluctuations [8–10]. Although the currently available COMT inhibitors, such as tolcapone and entacapone, can enhance the bioavailability of L-DOPA to a certain degree and improve motor function, certain safety and efficacy issues, including the hepatotoxicity of tolcapone [11] and the need for frequent dosing of entacapone [12, 13], have limited their use in clinical practice. Therefore, there is an unmet need for COMT inhibitors with a better therapeutic profile without increased safety risk.

To overcome the limitations with present COMT inhibitors, opicapone (OPC), a novel third-generation COMT inhibitor, was developed. It is a hydrophilic 1,2,4-oxadiazole derivative with a pyridine *N*-oxide residue at position 3 [14]. OPC is absorbed rapidly, predominantly distributed in the liver and kidney [15], and has an exceptionally high affinity (99.9%) for human plasma proteins [16]. OPC can be metabolized through different pathways, such as sulfation, methylation (by COMT), reduction, glucuronidation, and glutathione conjugation. Among them, sulfation is the primary metabolic pathway and BIA 9-1103 (OPC sulfate) is the major metabolite (inactive) of OPC [17, 18]. OPC could inhibit one of the two isoforms of COMT, namely the erythrocyte soluble COMT [S-COMT] [19], which is mainly

expressed in peripheral tissues such as liver, kidney, and erythrocytes. Therefore, the efficacy of OPC can be evaluated by erythrocyte S-COMT inhibition. Rocha et al. reported a maximum erythrocyte S-COMT inhibition (E_{\max}) in healthy male subjects ranging from 69.9% to 98.0% after repeated daily doses of 30 mg OPC [17].

OPC was first approved by the European Union (2016), followed by South Korea (2019), the USA, and Japan (2020). Falcão et al. found no obvious impact of ethnic factors on pharmacokinetics (PK) and pharmacodynamics (PD) profiles of OPC [20]. Besides, in a phase 1 study conducted by Xue et al., healthy Chinese and Caucasian subjects showed comparable PK characteristics of OPC after taking 50 mg OPC in multiple doses [21]. However, very little is known about the exposure–response and safety of OPC when given to the Chinese population. Hence, this study aimed to evaluate the PK and PD profiles of a single dose and multiple doses of OPC in healthy Chinese subjects and compare these parameters with those of matched Caucasian subjects, along with the assessment of safety and tolerability of OPC in healthy Chinese subjects. On the basis of the guidelines of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-E5 [22], we intended to perform the PK and PD comparisons between the two populations to help in making decisions about extrapolation of foreign clinical data in the Chinese population.

METHODS

Study Design

We conducted this open-label, single-center, phase 1, single ascending and once-daily repeated dose study (ChiCTR number CTR20192230) in healthy Chinese and Caucasian subjects at Beijing Hospital Clinical Trial Center (Beijing, China), in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP) and applicable regulatory requirements. The study protocol was approved by the ethics committee of Beijing Hospital (Beijing, China,

Approval number 2019BJYYEC-100-01). Written informed consent was obtained from each subject before participating in the study.

Study Population

Male and female healthy subjects (either Caucasian or Chinese) aged 18 to 45 years, with a body mass index (BMI) of 18.5 to 28 kg/m² and without clinically significant abnormalities in laboratory tests, electrocardiograms, and vital signs at screening, were included in the study. Subjects who met any of the following criteria were excluded: clinically significant illnesses or disorders; abnormalities in laboratory tests or physical examinations; being pregnant/lactating; a history of smoking/alcoholism; had an allergic or adverse reaction to related drugs (like tolcapone or entacapone); blood donation over 360 mL within 3 months before enrollment, taking any over-the-counter drugs/Chinese herbal medicines/vitamins within 7 days before enrollment; and any medical history or condition that may affect the safety or the in vivo process of the drug.

The sample size was estimated to meet the requirements of sample size in the Center for Drug Evaluation's 2005 technical guidelines for clinical pharmacokinetics research of chemical drugs [23].

Treatment

Eligible subjects were assigned to one of the three dosing groups (25, 50, and 100 mg OPC). The dose range was based on the previous phase 3 trials which showed that a 50-mg once-daily regimen had better efficacy and comparable safety in patients with Parkinson's disease than lower-dose regimens (i.e., 5 and 25 mg) [24, 25]. In addition, the US Food and Drug Administration has approved the 50-mg once-daily dose of OPC to be taken at bedtime in patients with Parkinson's disease [26]. The 25- and 50-mg groups recruited both Chinese and Caucasians, while the 100-mg group recruited only Chinese subjects. This was because of the difficulty of enrolling the Caucasians, and studying only 25-mg and 50-mg doses in

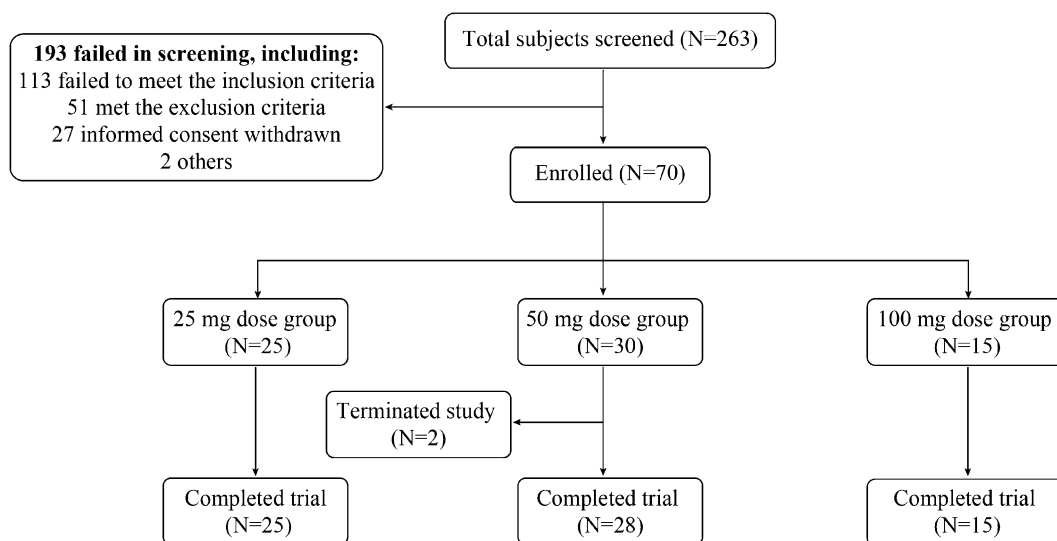


Fig. 1 Flowchart of sample disposition

Caucasians was considered adequate to detect sensitivity to ethnicity. The purpose of giving 100 mg to the Chinese population was to understand PK and PD parameters of OPC when given at a higher dose than recommended. Each subject received a single dose of OPC as per group allocation (25, 50, or 100 mg). To reveal both the single-dose and steady-state PK and PD characteristics of OPC, subjects in the 50-mg group received a single dose of OPC and an additional 50 mg OPC once daily for 10 consecutive days.

In the single-dose phase, all subjects received OPC on the morning of day 1 and were monitored at the clinical site for approximately 24 h post-dose and then discharged. On the morning of day 3 and day 4, they returned to the site for blood sample collection and safety assessments. In the multiple-dose phase, subjects in the 50-mg group continued to receive OPC once daily from day 5 to day 14. On day 12, they were readmitted to the clinical site and were discharged on day 20 after completing a 144-h assessment post last dose (day 14).

Sample Collection

Blood samples for PK analysis were collected within 1 h before the dose on day 1 and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, and 72 h post-dose in the single-dose phase; and within 1 h pre-dose on days 5, 12, 13, and 14 and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, and 144 h after the last dose in the multiple-dose phase. Blood samples for PD analysis were collected pre-dose on day 1 and at 0.5, 1, 2, 4, 6, 10, and 24 h post-dose in the single-dose phase; and pre-dose on day 14 and at 0.5, 1, 2, 4, 6, 10, 24, 48, 72, 96, 120, and 144 h after the last dose in the multiple-dose phase.

Bioanalytical Methods for PK and PD Analysis

Blood samples (6 mL at each point) were collected in ice-cold tubes containing potassium ethylenediaminetetraacetic acid (K₂EDTA), followed by centrifugation at 1500 × *g* at 4 °C for approximately 10 min. The resulting plasma was transferred into a collection tube. The remaining erythrocytes were washed three times under the same centrifugal conditions

Table 1 Summary of demographic data

Demographics		25 mg (N = 25)		50 mg (N = 30)		100 mg	Total
		Chinese subjects (N = 15)	Caucasian subjects (N = 10)	Chinese subjects (N = 15)	Caucasian subjects (N = 15)		
Sex, n (%)	Male	14 (93.3)	9 (90.0)	12 (80.0)	11 (73.3)	14 (93.3)	60 (85.7)
	Female	1 (6.7)	1 (10.0)	3 (20.0)	4 (26.7)	1 (6.7)	10 (14.3)
Age (years)	Mean ± SD	28.8 ± 6.5	27.5 ± 5.9	31.3 ± 6.6	25.1 ± 3.7	27.5 ± 5.3	28.1 ± 5.9
	Min, max	21, 44	20, 41	22, 40	19, 35	19, 38	19, 44
	Median (Q1, Q3)	27.0 (25.0, 32.0)	27.5 (24.0, 30.0)	32.0 (26.0, 39.0)	25.0 (23.0, 27.0)	28.0 (23.0, 31.0)	27.0 (24.0, 31.0)
Body weight (kg)	Mean ± SD	64.5 ± 8.1	69.0 ± 9.3	68.3 ± 8.4	71.6 ± 10.7	64.5 ± 10.4	67.5 ± 9.6
	Min, max	50.3, 76.5	54.5, 80.1	54.9, 81.5	49.8, 93.0	52.0, 88.4	49.8, 93.0
	Median (Q1, Q3)	64.8 (58.6, 72.2)	71.8 (59.9, 76.2)	67.8 (59.7, 75.4)	72.6 (66.1, 78.2)	62.7 (56.7, 68.0)	67.9 (59.3, 74.9)
Height (cm)	Mean ± SD	165.7 ± 5.4	172.8 ± 5.1	170.0 ± 8.4	173.6 ± 9.7	169.9 ± 7.3	170.2 ± 7.9
	Min, max	154.9, 175.5	164.8, 181.7	153.6, 180.6	148.8, 185.1	159.1, 185.2	148.8, 185.2
	Median (Q1, Q3)	165.2 (162.5, 170.0)	173.3 (169.7, 176.5)	170.4 (163.1, 177.8)	177.4 (168.4, 178.8)	168.8 (163.8, 173.3)	170.2 (164.8, 176.5)
BMI (kg/m ²)	Mean ± SD	23.5 ± 2.7	23.1 ± 2.6	23.6 ± 2.0	23.6 ± 1.8	22.2 ± 2.1	23.2 ± 2.2
	Min, max	19.4, 27.4	19.7, 26.5	20.1, 26.5	20.8, 27.6	19.6, 26.3	19.4, 27.6
	Median (Q1, Q3)	24.3 (21.1, 25.9)	22.7 (20.5, 25.5)	23.3 (21.8, 25.5)	23.7 (22.5, 24.5)	22.2 (20.5, 23.8)	23.0 (21.3, 25.0)

BMI body mass index, SD standard deviation, Q1 first quartile, Q3 third quartile

with twice the volume of ice-cold sodium chloride solution (0.9%). Both the plasma and washed erythrocytes were stored immediately at -70°C until shipment to a central lab.

Although BIA 9-1103 has no activity and safety risks, in a human mass balance study (unpublished data), it was observed that the exposure of BIA 9-1103 accounted for more than 50% of the total exposure; hence, the exposure of primary metabolite BIA 9-1103 was also evaluated. At the central lab, plasma concentrations of OPC and its major metabolite BIA 9-1103 were determined using liquid

chromatography–tandem mass spectrometry (LC–MS/MS). S-COMT assay was carried out using the washed erythrocytes in compliance with Good Laboratory Practice (GLP) at BIAL's Pharmacological Laboratory (S. Mamede do Coronado, Portugal) according to a validated method [27, 28]. The S-COMT activity was expressed as the amount of metanephrine (in picomoles) formed by the action of erythrocyte S-COMT upon epinephrine, per milligram of hemoglobin in the sample per hour [pmol/(mgHb/h)].

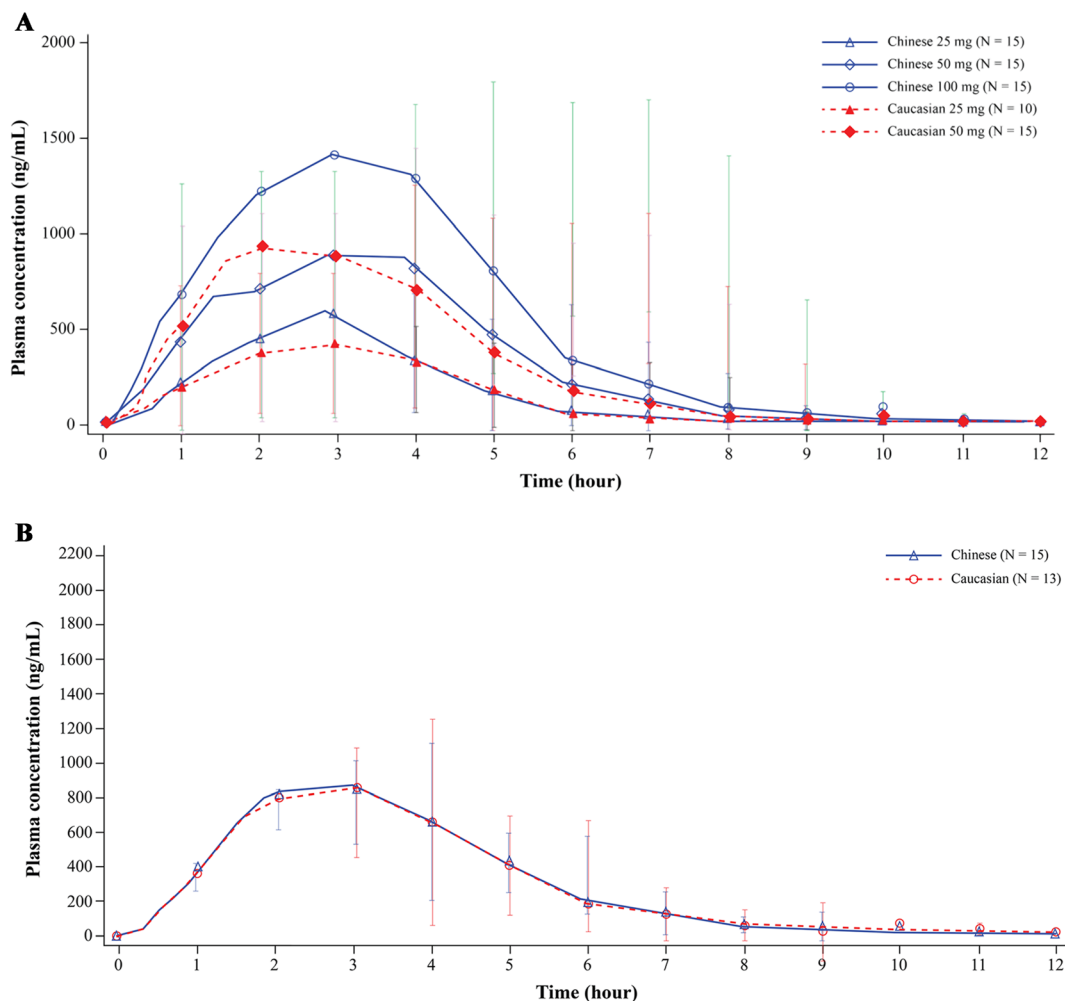


Fig. 2 Mean plasma concentration–time profiles: **a** opicapone single dose; **b** opicapone multiple dose; **c** BIA 9-1103 single dose; **d** BIA 9-1103 multiple dose. Error bars represent standard deviation

Pharmacokinetic Analysis

Parameters were calculated by non-compartmental analysis using WinNonlin® (Version 8.3, Pharsight Corporation, Mountain View, California, USA). The following PK parameters of OPC and BIA 9-1103, such as maximum observed plasma concentration (C_{max} , including $C_{max,ss}$), time to reach C_{max} (T_{max}), area under the plasma concentration–time curve (AUC, including AUC_{0-t} following a single dose and $AUC_{0-\tau}$ following multiple doses), the elimination half-life ($t_{1/2}$), the apparent clearance (CL/F), and the apparent

volume of distribution (V_d/F), were calculated from the individual plasma concentration versus time profiles.

Pharmacodynamics Analysis

The PD parameters derived from the individual S-COMT activity profiles using WinNonlin® included the S-COMT activity at maximum effect (E_{max}), time to reach E_{max} (TE_{max}), and area under the inhibition of S-COMT activity–time curve ($AUEC_{0-t}$, including $AUEC_{0-24h}$ following a single dose and $AUEC_{0-144h}$ following multiple doses). The maximum inhibition

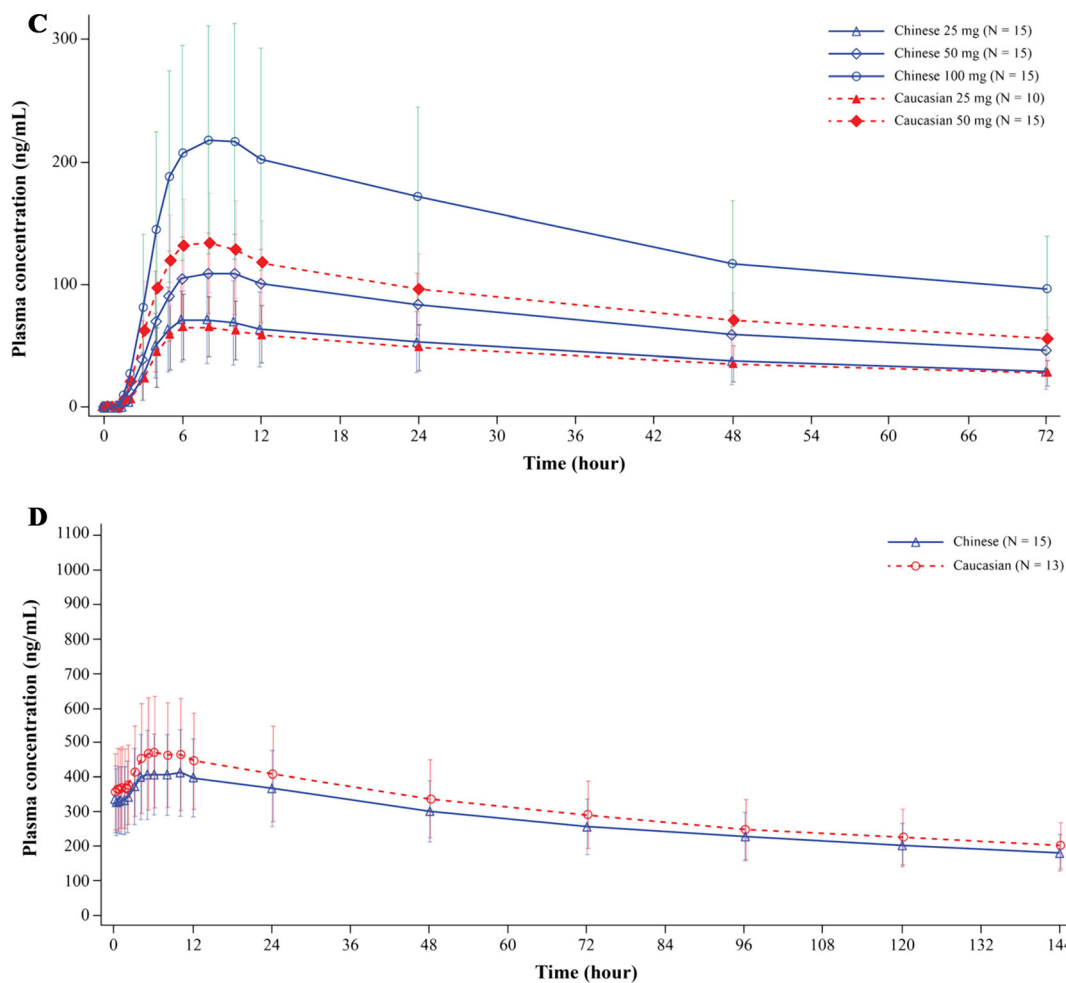


Fig. 2 continued

of S-COMT was calculated as $([E_0 - E_{max}] / E_0) \times 100\%$, where E_0 is the S-COMT activity at baseline before the first dose of OPC on day 1.

Safety Assessments

The safety and tolerability of OPC were evaluated throughout the study by assessing treatment-emergent adverse events (AEs), vital signs, laboratory results, physical examination findings, and a 12-lead electrocardiogram (ECG). AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA; version 23.0).

Statistical Analysis

SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) was used primarily to analyze PK and PD data of OPC in Chinese and Caucasian subjects after single-dose and multiple-dose administration. Demographics, PK, and PD parameters were summarized descriptively as per dosing groups. PK and PD parameters for each group are presented as mean (coefficient of variation [CV] %) or median (minimum, maximum), and were compared between Chinese and Caucasian subjects. The nonlinear mixed-effects modeling (NONMEM, version 7.4, ICON Development Solutions, USA) was used to set up a population PK model. One- and two-compartment models

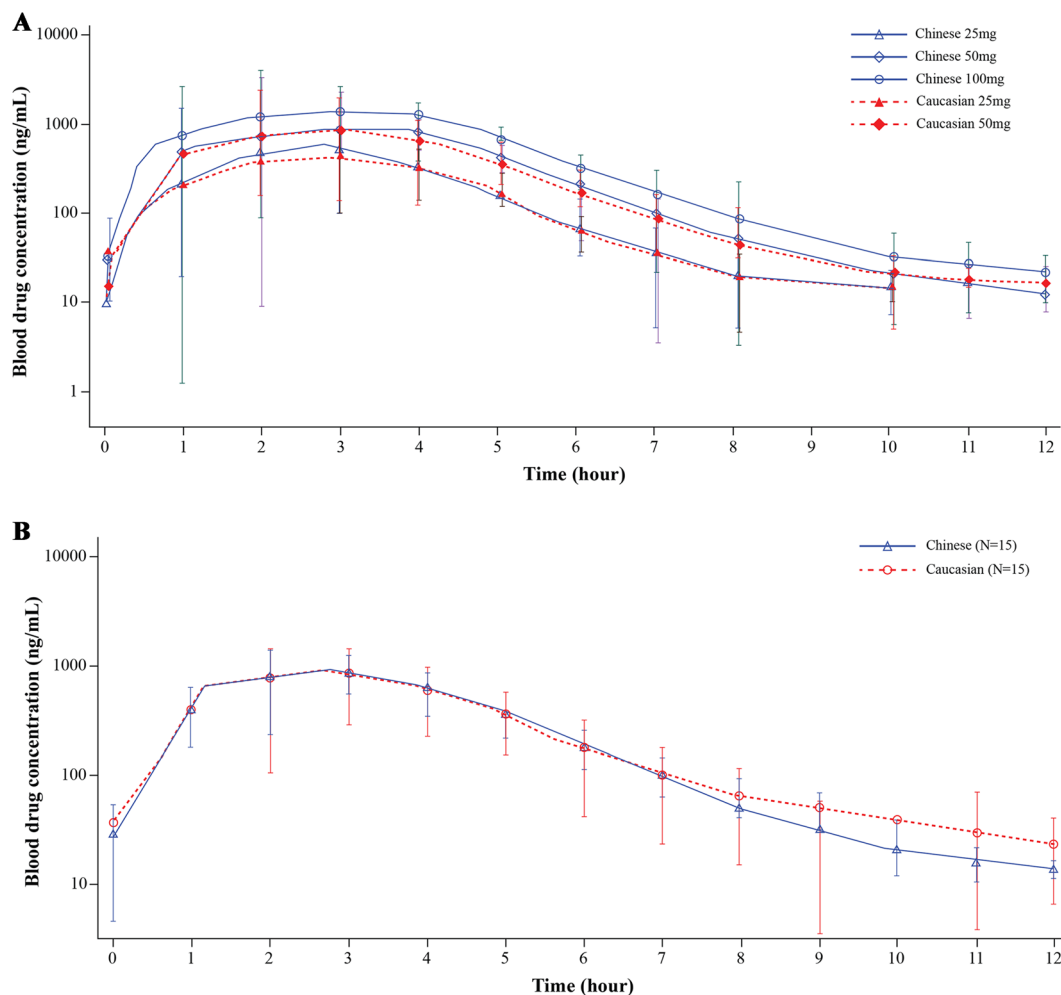


Fig. 3 Semi-logarithmic mean plasma concentration–time profiles: **a** opicapone single dose; **b** opicapone multiple doses; **c** BIA 9-1103 single dose; **d** BIA 9-1103 multiple dose. Error bars represent standard deviation

with two-phase absorption respectively best described the PK and PD of OPC and the PK of BIA 9-1103 in healthy Chinese and Caucasian subjects. Furthermore, race, gender, age, body weight, BMI, alanine aminotransferase, albumin, and creatinine were estimated in covariate analysis. The PK and PD model was evaluated using the goodness of fit plots and bootstrap method. Visual inspection was performed to assess the predictive ability of the final model. Moreover, the simulated PK and PD parameters along with the geometric mean ratios (GMRs; Chinese/Caucasian) and their 90% confidence intervals (CIs) were evaluated.

RESULTS

Demographic Characteristics of Subjects

In total, 70 eligible subjects (45 Chinese, 25 Caucasian) with a mean (SD) age of 28.1 (5.9) years and a mean BMI of 23.2 (2.2) kg/m² were enrolled in this study. The coronavirus disease (COVID-19) pandemic posed recruiting challenges; consequently, 10 Caucasian subjects, instead of 15, were recruited to the 25-mg group. The subjects' disposition is presented in Fig. 1 and detailed demographic characteristics of the eligible subjects and their group

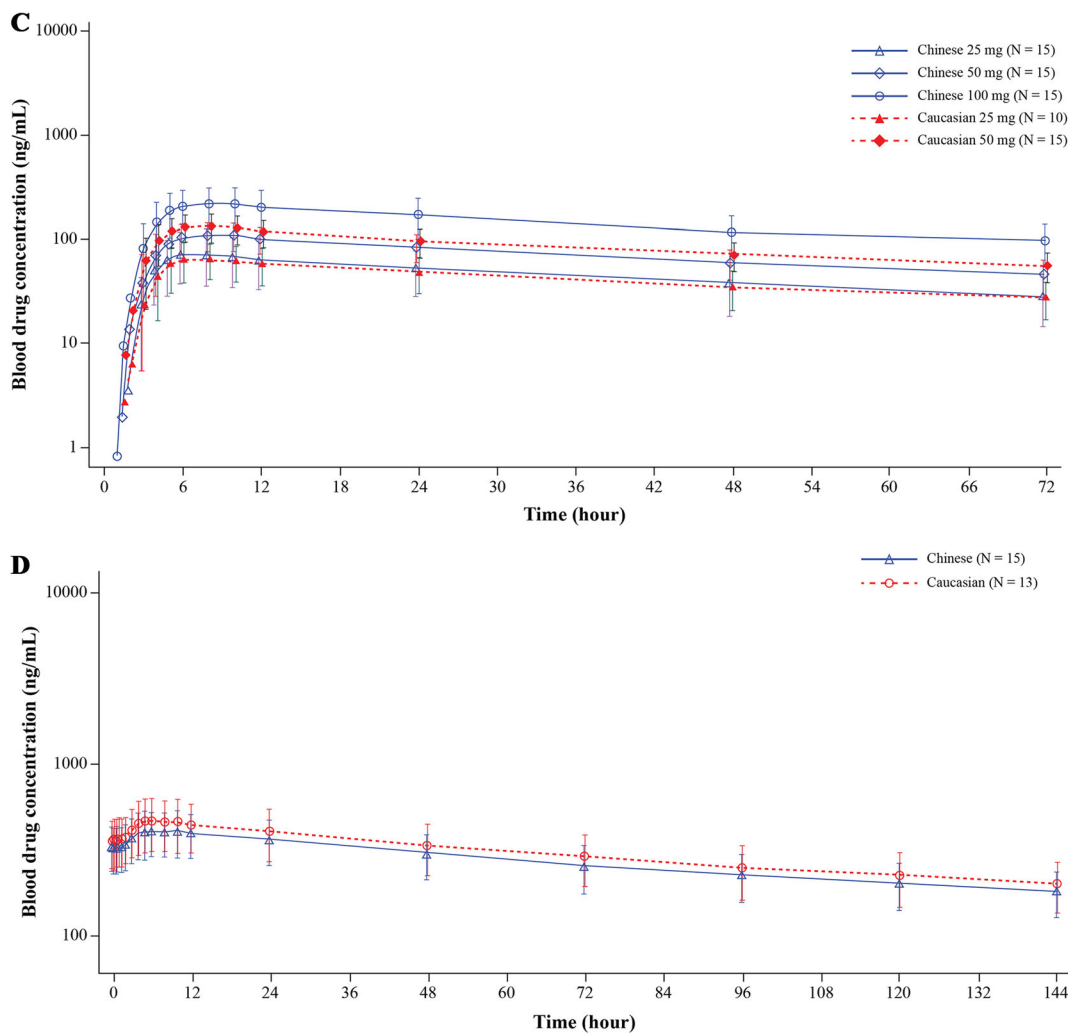


Fig. 3 continued

assignment are presented in Table 1. Overall, 68 subjects completed the study (two subjects discontinued because of adverse events). All subjects were included in the full analysis set and the PK, PD, and safety analysis sets.

Pharmacokinetics

The mean plasma concentration–time profiles and semi-logarithmic plasma concentration–time profiles of OPC and its major metabolite BIA 9-1103 are presented in Figs. 2 and 3, respectively. The trends of concentration–time curves were similar among different

groups and ethnicities, irrespective of the single- or multiple-dose administration. The key PK parameters of OPC and BIA 9-1103 after a single dose or multiple doses in Chinese and Caucasian subjects are summarized in Table 2. The C_{max} and AUC_{0-t} of both OPC and BIA 9-1103 showed a dose-dependent increase in both Chinese and Caucasians after single and multiple doses. For Chinese subjects, the mean C_{max} values of OPC after a single dose of 25 and 50 mg were 713.6 and 1210.5 ng/mL, respectively, whereas the mean AUC_{0-t} values were 1848.9 and 3875.2 h ng/mL, respectively. A similar trend was observed in Caucasian

Table 2 Pharmacokinetics parameters of opicapone and BIA 9-1103 after single- and multiple-dose administrations

Analytes	<i>N</i>	<i>t</i> _{max} (h)	<i>C</i> _{max} or <i>C</i> _{max,ss} (ng/ mL)	<i>C</i> _{min} (ng/ mL)	<i>AUC</i> _{0-<i>t</i>} (h ng/ mL)	<i>AUC</i> _{0-∞} or <i>AUC</i> _{0-<i>τ</i>} (h ng/ mL)	<i>V</i> _d / <i>F</i> (L)	<i>CL</i> / <i>F</i> (L/h)	<i>t</i> _{1/2} (h)
OPC (single dose)									
Chinese: 25 mg	15	3 (1.5–5)	713.6 (35.9)	–	1848.9 (41.8)	2100.1 (32.5)	13.4 (32.4)	13.3 (36.8)	0.7 (24.3)
50 mg	15	3 (1.5–4)	1210.5 (25.8)	–	3875.2 (30.7)	3913.8 (30.2)	21.8 (57.1)	13.8 (28.3)	1.1 (52.3)
100 mg	15	2 (1–5)	1898.0 (23.4)	–	6205.1 (30.9)	6243.7 (30.9)	32.1 (29.4)	17.9 (37.9)	1.3 (26.1)
Caucasian: 25 mg	10	3 (0.75–5)	556.3 (35.7)	–	1622.8 (24.7)	1728.3 (19.5)	15.0 (26.2)	15.0 (20.3)	0.7 (17.0)
50 mg	15	2 (1–4.02)	1327.8 (31.8)	–	3802.1 (29.2)	3823.9 (29.1)	17.4 (22.6)	14.2 (30.9)	0.9 (30.6)
BIA 9-1103 (single dose)									
Chinese: 25 mg	15	6 (5–12)	75.0 (48.2)	–	3169.4 (48.9)	5402.5 (50.8)	446.0 (50.7)	6.1 (56.9)	52.6 (12.3)
50 mg	15	8 (5–10)	112.3 (29.7)	–	4990.2 (32.0)	8630.2 (38.8)	476.6 (22.3)	6.5 (30.4)	52.8 (13.4)
100 mg	15	8 (5–10)	224.1 (43.1)	–	10,084.4 (43.0)	17,712.8(44.2)	542.7 (50.6)	6.9 (47.6)	54.7 (9.1)
Caucasian: 25 mg	10	7 (5–10)	68.3 (37.2)	–	2950.9 (40.5)	5290.4 (40.3)	453.3 (37.4)	5.5 (40.4)	58.0 (11.9)
50 mg	15	6 (4–8)	139.0 (31.1)	–	5935.5 (30.1)	10,801.3 (31.8)	433.5 (28.7)	5.1 (32.8)	59.9 (14.1)
OPC (multiple doses)									
Chinese: 50 mg	15	2.4 (1–4)	1127.7 (24.6)	*0.0 (–)	–	3594.8 (20.8)	–	–	1.3 (32.6)
Caucasian: 50 mg	13	3.0 (1.5–5.0)	1208.4 (39.5)	*0.0 (–)	–	3797.3 (29.5)	–	–	1.6 (44.1)
BIA 9-1103 (multiple doses)									
Chinese: 50 mg	15	6 (4–12)	423.3 (29.9)	319.7 (30.2)	–	9252.6 (29.1)	–	–	137.2 (29.3)

Table 2 continued

Analytes	<i>N</i>	<i>t</i> _{max} (h)	<i>C</i> _{max} or <i>C</i> _{max,ss} (ng/ mL)	<i>C</i> _{min} (ng/ mL)	<i>AUC</i> _{0–<i>t</i>} (h ng/ mL)	<i>AUC</i> _{0–∞} or <i>AUC</i> _{0–<i>τ</i>} (h ng/ mL)	<i>V</i> _d / <i>F</i> (L)	<i>CL</i> / <i>F</i> (L/h)	<i>t</i> _{1/2} (h)
Caucasian: 50 mg	13	6 (4–12)	493.2 (32.6)	344.6 (31.2)	–	10,414.1 (32.4)	–	–	124.5 (14.7)

*AUC*_{0–*t*} area under the plasma concentration–time curve from time 0 to the last sampling time with concentrations above the lower limit of quantitation, *AUC*_{0–∞} area under the plasma concentration–time curve from time 0 to infinity, *AUC*_{0–*τ*} area under the plasma concentration–time curve over the dosing interval, *C*_{max} maximum observed plasma concentration, *C*_{max,ss} *C*_{max} in steady state, *C*_{min} minimum plasma concentration, *CL*/*F* apparent volume of the central compartment cleared of drug per unit time, *OPC* opicapone, *t*_{1/2} terminal plasma half-life

Data for *t*_{max} are presented as median (min, max); other data are presented as mean (coefficient of variation, %); *Represents below the limit of quantification (BLQ)

subjects; the mean *C*_{max} values of OPC after a single dose of 25 and 50 mg were 556.3 and 1327.8 ng/mL, respectively, and the mean *AUC*_{0–*t*} values were 1622.8 and 3802.1 h ng/mL, respectively. The clearance was consistent with all doses (Table 2). The key plasma PK parameters of OPC and BIA 9-1103 were compared between Chinese and Caucasian subjects following single and multiple doses. The point estimates of GMRs (Chinese/Caucasian) for key parameters (i.e., *C*_{max} or *C*_{max,ss} and *AUC*_{0–*t*} or *AUC*_{0–*τ*}) all fell between 80% and 125% (Table 3).

Pharmacodynamics

Figure 4 depicts the changes in the S-COMT activity over time after taking single or multiple doses of OPC. The inhibitory effect on S-COMT was observed immediately after taking OPC orally in all groups, which reached the maximum at about 4 h post-dose and then gradually decreased but did not return to the baseline level. During the multiple-dose phase, the activity of S-COMT was continuously inhibited. No apparent differences were observed in the inhibitory effect of OPC between Chinese and Caucasian subjects in the same dosing group. After administration of a single dose of OPC, the maximum inhibition of S-COMT and *AUEC*_{0–24h} increased as the dose rose from 25 to 100 mg in Chinese subjects (the maximum

S-COMT inhibition 82.7–95.2%, *AUEC*_{0–24h} 1475.9–1825.8% h) and from 25 to 50 mg in Caucasian subjects (the maximum S-COMT inhibition 79.7–91.2%, *AUEC*_{0–24h} 1472.7–1738.3% h; Table 4).

The maximum percentage inhibition values of S-COMT after single vs multiple administrations of OPC in 50-mg dose groups in Chinese and Caucasian subjects were 90.3% vs 94.3% and 91.2% vs 94.4%, respectively. Similarly, *AUEC*_{0–24h} values in single-dose administration vs *AUEC*_{0–144h} in multiple dose administrations of OPC 50-mg dose groups were 1742.5 vs 8612.0% h and 1738.3 vs 7919.1% h in Chinese and Caucasians, respectively. After administration of multiple doses of 50 mg OPC, the maximum inhibition of S-COMT, *E*_{max}, and *AUEC*_{0–144h} were similar in both Chinese and Caucasian subjects. The 90% CIs of GMRs for *E*_{max} and *AUEC*_{0–*t*} (*AUEC*_{0–24h} or *AUEC*_{0–144h}) in both phases all fell between 80% and 125% (Table 5), which matches the earlier PK results.

Safety and Tolerability

In total, 17 subjects (24.3%) experienced 23 AEs during the study, most of which were mild in severity and were self-limited. Only two AEs experienced by two Caucasian subjects were moderate in intensity [presyncope (50 mg group, considered possibly related to the administration of OPC) and the elevated

Table 3 Comparison of pharmacokinetic parameters of opicapone and BIA 9-1103 after single- and multiple-dose administrations

Parameter	N	GM (LSM)	GMR (Chinese/Caucasian; %)	90% CI of GMR
OPC				
Single dose (25 mg)				
C_{\max} (ng/mL)				
Chinese	15	444.1	109.2	86.5–137.7
Caucasian	10	406.8		
AUC_{0-t} (h ng/mL)				
Chinese	15	1552.4	105.1	88.4–124.9
Caucasian	10	1477.7		
$AUC_{0-\infty}$ (h ng/mL)				
Chinese	15	1555.0	105.1	88.4–124.9
Caucasian	10	1480.2		
Single dose (50 mg)				
C_{\max} (ng/mL)				
Chinese	15	917.2	93.4	77.0–113.3
Caucasian	15	981.9		
AUC_{0-t} (h ng/mL)				
Chinese	15	3638.5	101.8	86.5–119.9
Caucasian	15	3574.0		
$AUC_{0-\infty}$ (h ng/mL)				
Chinese	15	3644.5	101.8	86.5–119.9
Caucasian	15	3580.0		
Multiple doses (50 mg)				
$C_{\max,ss}$ (ng/mL)				
Chinese	15	921.5	88.4	72.6–107.5
Caucasian	13 ^a	1042.9		
$AUC_{0-\tau}$ (h ng/mL)				
Chinese	15	3646.9	96.7	82.4–113.6
Caucasian	13 ^a	3769.8		
BIA 9-1103				
Single dose (25 mg)				
C_{\max} (ng/mL)				

Table 3 continued

Parameter	N	GM (LSM)	GMR (Chinese/Caucasian; %)	90% CI of GMR
Chinese	15	62.1	105.9	78.4–143.2
Caucasian	10	58.62		
AUC _{0–t} (h ng/mL)				
Chinese	15	2886.0	106.2	78.5–143.5
Caucasian	10	2718.6		
Single dose (50 mg)				
<i>C</i> _{max} (ng/mL)				
Chinese	15	100.9	88.2	73.5–106.0
Caucasian	15	114.2		
AUC _{0–t} (h ng/mL)				
Chinese	15	4680.2	88.1	73.4–105.9
Caucasian	15	5310.7		
Multiple doses (50 mg)				
<i>C</i> _{max,ss} (ng/mL)				
Chinese	15	403.7	90.6	74.8–109.7
Caucasian	13 ^a	445.8		
AUC _{0–τ} (h ng/mL)				
Chinese	15	8854.7	90.7	74.9–109.8
Caucasian	13 ^a	9766.1		

AUC_{0–t} area under the plasma concentration–time curve from time 0 to the last sampling time with concentrations above the lower limit of quantitation, AUC_{0–∞} area under the plasma concentration–time curve from time 0 to infinity, AUC_{0–τ} area under the plasma concentration–time curve over the dosing interval, *C*_{max} maximum observed plasma concentration, *C*_{max,ss} *C*_{max} in steady state, *CI* confidence interval, *LSM* least-square mean, *GM* geometric mean, *GMR* geometric mean ratio, *OPC* opicapone, *PK* pharmacokinetics

^aTwo Caucasians discontinued treatment because of adverse events

total bilirubin level (25 mg group, considered unlikely related to the use of OPC)]. Only four adverse drug reactions (ADRs) were reported by three subjects (4.3%), which were presyncope (1.4%), hyperhidrosis (1.4%), belching (1.4%), and bloating (1.4%). No serious adverse events (SAEs) or death occurred. Two Caucasian subjects dropped out of the study because of AEs [presyncope (50 mg group, considered possibly related to the administration of OPC) and an increase in blood creatine phosphokinase level

(50 mg group, considered unlikely related to the use of OPC); Supplementary Table 1]. No clinically significant findings related to OPC were observed in laboratory tests, vital signs, physical examinations, and 12-lead ECGs. Overall, a lower incidence of AEs was observed in Chinese subjects compared with Caucasian subjects; however, the numbers were generally low.

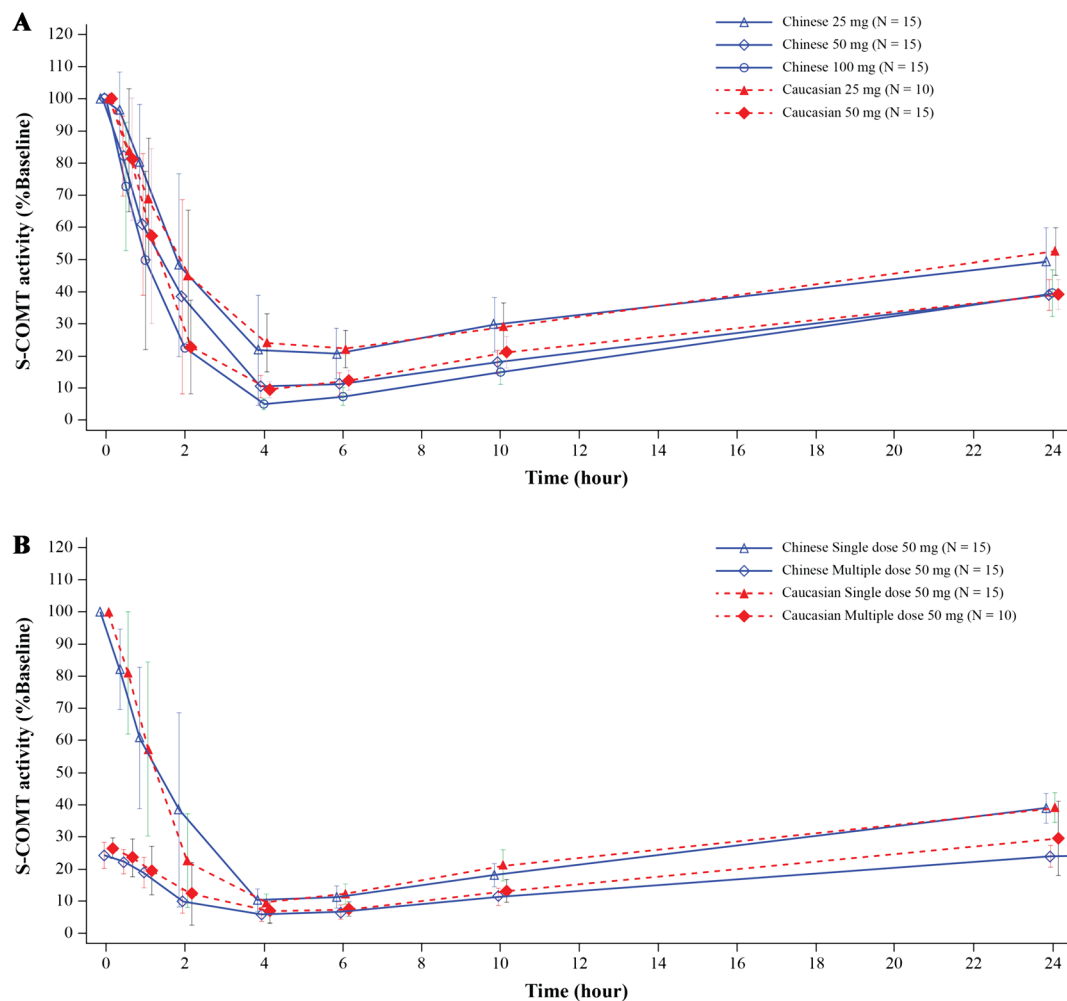


Fig. 4 Mean S-COMT activity–time profiles as a percentage of change concerning baseline after **a** single dose; **b** multiple doses. Error bars represent standard deviation. S-COMT, erythrocyte-soluble catechol-*O*-methyltransferase

DISCUSSION

The number of individuals diagnosed with Parkinson's disease is likely to grow substantially in the coming years. By 2030, the number of Chinese patients with Parkinson's disease is estimated to reach 4.94 million, accounting for half of the patients with Parkinson's disease worldwide [29]. OPC was recommended by Chinese guidelines for the treatment of Parkinson's disease (4th edition) as adjunctive treatment to levodopa/carbidopa [10]. However, it is still not available in China, despite the impending clinical need. Several studies have

demonstrated the efficacy of OPC in Caucasian patients with Parkinson's disease [24, 25]. We, therefore, designed this study to evaluate whether OPC has comparable and bioequivalent PK and PD characteristics and effects between Chinese and Caucasians and provide further evidence for extrapolation of the foreign clinical data to China.

In the present study, the plasma exposure (C_{max} and AUC) of OPC and its metabolite BIA 9-1103 increased with the increase in the dose (25 mg, 50 mg, and 100 mg). The t_{max} of OPC in Chinese and Caucasian subjects ranged from 2 to 3 h, and the average $t_{1/2}$ ranged

Table 4 Pharmacodynamic parameters of S-COMT after single- and multiple-dose administrations

	<i>N</i>	E_0 [pmol/(mgHb/h)]	E_{max} [pmol/(mgHb/h)]	TE_{max} (h)	$([E_0 - E_{max}]/E_0) \cdot 100$ (%)	$AUEC_{0-t}$ (%·h)
Single dose						
Chinese: 25 mg	15	15.8 (29.11)	2.7 (51.8)	4.5 (20)	82.7 (7.9)	1475.9 (13.6)
50 mg	15	12.5 (32)	1.1 (27.3)	4.7 (19.1)	90.3 (3.3)	1742.5 (6.5)
100 mg	15	13.0 (35.4)	0.5 (40)	3.9 (23.1)	95.2 (1.9)	1825.8 (5.8)
Caucasian: 25 mg	10	15.7 (40.8)	3.3 (54.5)	4.8 (29.2)	79.7 (6.0)	1472.7 (8.97)
50 mg	15	10.7 (36.4)	0.9 (44)	3.7 (32.4)	91.2 (2.6)	1738.3 (4.6)
Multiple doses						
Chinese: 50 mg	15	12.5 (32)	0.6 (33.3)	4.3 (23.3)	94.3 (2.1)	8612.0 (7.6)
Caucasian: 50 mg	10	10.7 (36.4)	0.6 (66.7)	4.3 (30.2)	94.4 (2.1)	7919.1 (12.0)

$AUEC_{0-t}$ area under the inhibition of S-COMT activity–time curve from time 0 to the last sampling time with concentrations above the lower limit of quantitation, E_0 S-COMT activity at baseline, E_{max} maximum S-COMT activity post-dose administration; $([E_0 - E_{max}]/E_0) \cdot 100$, the maximum percentage inhibition of S-COMT activity, *PD* pharmacodynamic, *S-COMT* erythrocyte-soluble catechol-*O*-methyltransferase, TE_{max} time to reach E_{max} . Data are presented as mean (coefficient of variation, %). $AUEC_{0-t}$ was $AUEC_{0-24h}$ for single dose and $AUEC_{0-144h}$ for multiple doses

between 0.7 and 1.3 h while the t_{max} of BIA 9-1103 ranged from 6 to 8 h and the average $t_{1/2}$ ranged from 52 to 58 h. The PK characteristics of different dose groups were observed to be similar post-single-dose administration. Also, the metabolic characteristics of OPC with multiple administration for 10 days (50 mg) were found to be similar to that of single administration and no accumulation was observed. After single and multiple administration, the overall PK parameters were found to be similar in Chinese and Caucasians.

There is a causal relationship between exposure to a medication and its therapeutic activity. Evaluation of PD and PK parameters helps to integrate quantitative information about the pharmacologic properties of a compound with its PK [30]. We observed an exposure-related

increase in S-COMT inhibition. After a single-dose administration of 25, 50, and 100 mg OPC, the C_{max} and the maximum inhibition rates of S-COMT were 713.6, 1210.5, and 1898.0 ng/mL and 82.7%, 90.3%, and 95.2%, respectively in Chinese subjects, and after single-dose administration of 25 and 50 mg OPC in Caucasians, the values were 556.3 and 1327.8 ng/mL, and 79.7% and 91.2%, respectively. Our results were consistent with a previous study (in which OPC was used in the range of 10–1200 mg) where a dose-dependent and long-lasting S-COMT inhibitory effect was reported, wherein the maximum and the 72-h post-dose S-COMT inhibition values were in the range of 34.5% (10 mg) to 100% (1200 mg) and 5.9% (10 mg) to 54.6% (800 mg), respectively [18]. Similarly, in a multiple-dose escalating study, where OPC 5 to

Table 5 Comparison of pharmacodynamic parameters of S-COMT after single- and multiple-dose administrations

Chinese/Caucasian	<i>N</i>	GM (LSM)	GMR (Chinese/Caucasian; %)	90% CI of GMR
Single dose (25 mg)				
<i>E</i> _{max}				
Chinese	15	70.1	97.1	92.3–102.1
Caucasian	10	72.2		
AUEC _{0–24h}				
Chinese	15	1349.7	97.6	92.9–102.6
Caucasian	10	1382.2		
Single dose (50 mg)				
<i>E</i> _{max}				
Chinese	15	87.3	98.5	95.1–102.1
Caucasian	15	88.6		
AUEC _{0–24h}				
Chinese	15	1686.5	100.2	97.3–103.2
Caucasian	15	1683.2		
Multiple doses (50 mg)				
<i>E</i> _{max}				
Chinese	15	99.9	99.8	96.9–102.8
Caucasian	13*	100.1		
AUEC _{0–144h}				
Chinese	15	8523.8	105.9	101.5–110.4
Caucasian	13*	8051.0		

CI confidence interval, LSM least-square mean, GM geometric mean, GMR geometric mean ratio, S-COMT erythrocyte-soluble catechol-*O*-methyltransferase

30 mg was administrated in healthy subjects for 8 consecutive days, the PK and PD profiles were closely related to the administered dose as systemic exposure increased in approximately dose-proportional manner. Compared with a single dose, the inhibition of S-COMT lasted longer after the administration of multiple doses of OPC, with an inhibition ranging from 16.33% (5 mg) to 20.3% (30 mg) 144 h after the last dose [17]. Moreover, a dose-dependent increase in clinical outcomes was observed in phase 3 studies by Ferreira et al. and Lees et al.

[24, 25] demonstrating a relationship between exposure and therapeutic activity of OPC.

The PK and PD of drugs can be influenced by ethnicity which may further influence the dosage, efficacy, and safety of the drug in different regions. Hence, we further evaluated the effect of ethnicity on PK and PD profiles of OPC. From the results, the point estimates of GMRs (Chinese/Caucasian) were close to 100.0%, and 90% CI of most of the PK and PD parameters of OPC, except the 90% CI of *C*_{max} in 25 and 50 mg, fell within the range of 80% to 125%,

indicating no significant differences in PK and PD profiles between Chinese and Caucasian subjects. So, we can conclude that no sensitivity to ethnicity exists as indicated by similar PK and PD characteristics. The large width or large variability reflected in 90% CI of the PK and PD parameters may be due to the parallel design (instead of a cross-over) inducing between-subject variability in the comparison, and also due to the low and imbalanced number of subjects between Chinese and Caucasian 25-mg dose groups. These findings were consistent with a previous multiple ascending dose study ($N = 38$). After administration of OPC (5-, 25-, or 50 mg capsules) once daily for 10 days, comparable PK and PD profiles were reported between the healthy Japanese and matched white subjects [20]. The PK profiles of the present study and the Japanese study were comparable. The C_{max} and AUC_{0-t} obtained in the present study among Caucasians with 25 mg (556.3 ng/mL and 1622.8 h ng/mL, respectively) and 50 mg (1327.8 ng/mL and 3802.1 h ng/mL, respectively) were slightly lower than the values in the Japanese study (25 mg: 794 ng/mL and 2013 h ng/mL, respectively; 50 mg: 1540 ng/mL and 3727 h ng/mL, respectively). The C_{max} and AUC_{0-t} reported in Chinese volunteers in the present study at 25 mg (713.6 ng/mL and 1848.9 h ng/mL, respectively) were similar to the values reported in Japanese patients (797 ng/mL and 1886 h ng/mL, respectively) but slightly higher values were reported with the 50-mg dose in Japanese patients (1736 ng/mL and 4438 h ng/mL, respectively).

Our results revealed a lower incidence of AEs in Chinese compared with Caucasian subjects. ADRs reported in our study included presyncope, hyperhidrosis, belching, and bloating. No new risks or safety concerns were identified in this study.

Our study was the first clinical study to evaluate the PK, PD, and safety parameters of OPC in the Chinese population. Our results showed that OPC is not sensitive to ethnicity; hence, this study could be a bridging study and, to a certain extent, supported the extrapolation of clinical data from Caucasians to Chinese. OPC may serve as a new promising therapeutic

option for Parkinson's disease in China. There are some limitations of our study. First, the number of Caucasian subjects in the 25-mg group was less than planned. Thus, the assessment of ethnic differences may not be adequate. Second, as a short-term phase 1 study, the safety profile of OPC could not be fully captured, and the long-term safety of OPC was left uninvestigated. In addition, a high screening failure rate was observed because of the COVID-19 pandemic. Safety monitoring and assessment of OPC in a larger population is warranted, which may provide further insights.

CONCLUSIONS

Ethnicity had no significant impacts on PK and PD profiles in Chinese and Caucasian subjects after taking single or multiple doses of OPC. OPC was safe and well tolerated in healthy Chinese subjects.

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Compliance with Ethics Guidelines. The study protocol was reviewed and approved by the ethics committee of Beijing Hospital (Beijing, China, Approval number 2019BJYYEC-100-01). Written informed consent was obtained from each subject before participating in the study. All authors confirm that our study was performed following the Good Clinical Practice (GCP) as well as the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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