British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 2422–2432 2422

ORIGINAL ARTICLE

Pharmacokinetics, metabolism and safety of deuterated L-DOPA (SD-1077)/carbidopa compared to L-DOPA/carbidopa following single oral dose administration in healthy subjects

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Received 17 January 2018; **Revised** 12 June 2018; **Accepted** 22 June 2018

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Keywords deuterated, deuterium, L-DOPA, metabolism, Parkinson's disease, pharmacokinetics, SD-1077

AIMS

SD-1077, a selectively deuterated precursor of dopamine (DA) structurally related to L-3,4-dihydroxyphenylalanine (L-DOPA), is under development for treatment of motor symptoms of Parkinson's disease. Preclinical models have shown slower metabolism of central deuterated DA. The present study investigated the peripheral pharmacokinetics (PK), metabolism and safety of SD-1077.

METHODS

Plasma and urine PK of drug and metabolites and safety after a single oral 150 mg SD-1077 dose were compared to 150 mg L-DOPA, each in combination with 37.5 mg carbidopa (CD) in a double-blind, two-period, crossover study in healthy volunteers ($n = 16$).

RESULTS

Geometric least squares mean ratios (GMRs) and 90% confidence intervals (90% CI) of SD-1077 *vs.* L-DOPA for C_{max}, AUC_{0-t}, and AUC_{0-inf} were 88.4 (75.9–103.1), 89.5 (84.1–95.3), and 89.6 (84.2–95.4), respectively. Systemic exposure to DA was significantly higher after SD-1077/CD compared to that after L-DOPA/CD, with GMRs (90% CI) of 1.8 (1.45–2.24; $P = 0.0005$) and 2.06 (1.68–2.52; $P < 0.0001$) for C_{max} and AUC_{0-t} and a concomitant reduction in the ratio of 3,4-dihydroxyphenylacetic acid/DA confirming slower metabolic breakdown of DA by monoamine oxidase (MAO). There were increases in systemic exposures to metabolites of catechol O-methyltransferase (COMT) reaction, 3-methoxytyramine (3-MT) and 3-O-methyldopa (3-OMD) with

DOI:10.1111/bcp.13702

GMRs (90% CI) for SD-1077/CD to L-DOPA/CD for 3-MT exposure of 1.33 (1.14–1.56; $P = 0.0077$) and 1.66 (1.42–1.93; $P < 0.0001$) for C_{max} and AUC_{0-t}, respectively and GMRs (90% CI) for 3-OMD of 1.19 (1.15, 1.23; $P < 0.0001$) and 1.31 (1.27, 1.36; $P < 0.0001$) for C_{max} and AUC_{0-t}. SD-1077/CD exhibited comparable tolerability and safety to L-DOPA/CD.

CONCLUSIONS

SD-1077/CD demonstrated the potential to prolong exposure to central DA at comparable peripheral PK and safety to the reference L-DOPA/CD combination. A single dose of SD-1077 is safe for further clinical development in Parkinson's disease patients.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- SD-1077 is a selectively deuterated precursor of dopamine structurally related to L-3,4-dihydroxyphenylalanine (L-DOPA) for treatment of the motor symptoms of Parkinson's disease**.**
- Animal studies showed that deuteration at α- and β-carbon slowed down the breakdown of deuterated dopamine by monoamine oxidase and dopamine β-hydroxylase with corresponding motor effects.

WHAT THIS STUDY ADDS

- The selective deuteration in SD-1077 attenuates the metabolic degradation of the deuterated dopamine in plasma relative to L-DOPA in healthy subjects co-administered carbidopa.
- Peripheral PK and safety following a single oral dose of SD-1077/carbidopa and L-DOPA/carbidopa is comparable in healthy subjects.

Introduction

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease, affecting over 6 million patients worldwide [1]. PD is associated with dopaminergic neuronal loss, which produces a progressive decrease in dopamine levels within the striatum [2]. Despite available treatment approaches, PD continues to significantly affect health-related quality of life, activities of daily living, loss of employment and increased patient morbidity and mortality [3, 4].

L-3,4-dihydroxyphenylalanine (**L-DOPA**), the precursor to **dopamine** (DA), in combination with a peripheral DOPA decarboxylase (**DDC**) inhibitor remains the standard symptomatic therapy for Parkinson's disease. Peripheral DDC inhibitors reduce peripheral conversion of L-DOPA to DA thereby reducing side effects, such as nausea and vomiting, and increasing DA's half-life and availability to the brain [5]. The peripheral and central metabolism of L-DOPA and DA follows the same scheme (Figure 1) but the turnover is different because of the involvement of different compartments and different expression of the involved enzymes.

Following active transport of L-DOPA into the brain, DDC catalyzes the formation of DA, which is stored in vesicles until release into the synaptic cleft. Part of DA is recycled by reuptake into the cell and vesicles. The second major metabolic pathway of L-DOPA is methylation by catechol O-methyltransferase (**COMT**) to 3-OMD. DA is mainly metabolized by monoamine oxidase (MAO) and to a lesser extent by dopamine β-hydroxylase (**DBH**) and COMT. MAO catalyzes the oxidation of DA to 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is further oxidized by aldehyde dehydrogenase to 3,4-dihydroxyphenylacetic acid (DOPAC) and in a final step converted by COMT to homovanillic acid (HVA). DBH catalyzes the formation of the active metabolite **norepinephrine**. Methylation of DA by COMT leads to the formation of 3-methoxytyramine (3-MT) that is further metabolized by MAO and aldehyde dehydrogenase to HVA. Metabolites from peripheral and central degradation are mainly excreted via urine [6].

Long-term use of L-DOPA in combination with DDC inhibitors inevitably leads to treatment-induced motor complications, including wearing off, ON/OFF phenomena, delayed on, freezing, dystonia and dyskinesia [7]. Causes of these motor complications are unknown but are thought to involve central and peripheral mechanisms [8]. One of the proposed central mechanisms relate to the pulsatile stimulation of postsynaptic receptors caused by the short half-life of L-DOPA therapy paired with presynaptic nigrostriatal neuronal degeneration; the aberrant release of converted L-DOPA as a *false* neurotransmitter by serotoninergic neurons, plasticity changes resulting in alterations in the sensitivity of postsynaptic dopamine receptors to released DA and increased glutamatergic release in the striatum. The peripheral mechanisms involve Parkinson's disease-related reduced gastric emptying and the competition of L-DOPA with dietary amino acids for transfer across the blood–brain barrier.

In contrast to methods that improve the peripheral exposure of L-DOPA [9], selective deuteration of L-DOPA (**D3 L-DOPA**) was performed with the aim to slow down the metabolic breakdown of the deuterated DA metabolized from the deuterated precursor in the brain by exploiting a primary kinetic isotope effect as described by Wilberg in 1955 [10]. The selective deuteration of SD-1077 is aimed at reduced degradation of central DA without a change in metabolic pathway, which has been reported for other deuterated drugs [11–13]. Specific sites for deuterium substitution were selected based on previously demonstrated slower oxidative deamination of DA by MAO and slower formation of norepinephrine by DBH when deuterium is incorporated at the α-carbon [14] and β-carbon [15] respectively. The surface charge and spatial characteristics of deuterated drugs and

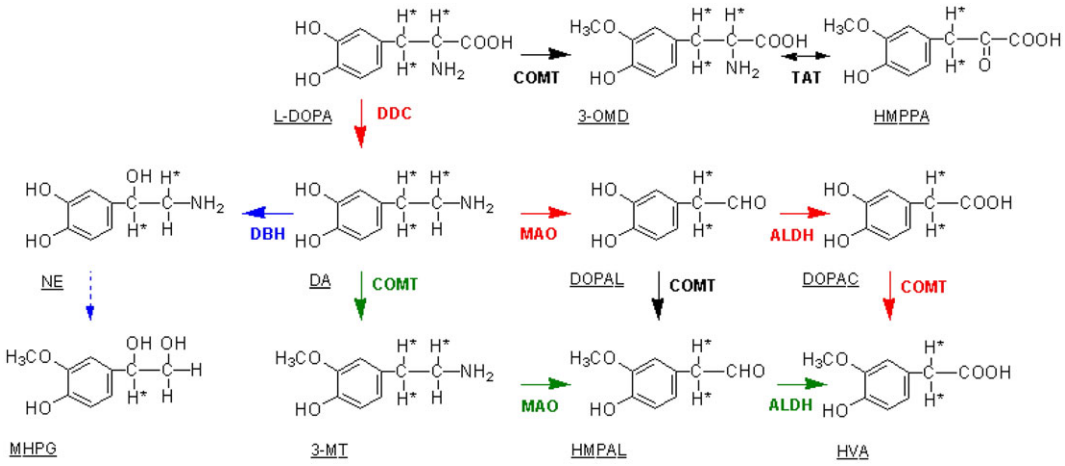

Figure 1

Metabolism of L-DOPA and SD-1077. *Deuterated positions in SD-1077. Abbreviations include 3-OMD, 3-O-methyldopa; ALDH, aldehyde dehydrogenase; COMT, catechol O-methyltransferase; DA, dopamine; DBH, dopamine β-hydroxylase; DDC, DOPA decarboxylase; DOPAL, 3,4-dihydroxyphenylacetaldehyde; DOPAC, 3,4-dihydroxyphenylacetic acid; HMPPA, 4-hydroxy-3-methoxyphenylpyruvic acid; HMPAL, 4-hydroxy-3-methoxyphenyl acetaldehyde; HVA, homovanillic acid; L-DOPA, L-3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; MHPG, 3-methoxy-4-hydroxyphenylglycol; NE, norepinephrine; TAT, tyrosine aminotransferase

their metabolites have been shown to be biologically indistinguishable from their nondeuterated forms [16, 17] and there were no differences in the binding profile of regular DA and deuterated DA to any DA receptor subtype or to the transporter as evaluated by radioligand binding assays [18]. The manufacture of SD-1077, a selectively deuterated drug in clinical development for the treatment of the motor symptoms of Parkinson's disease, yields 90% d_3-(2S)-2-amino-2,3,3-trideuterio-3-(3,4-dihydroxyphenyl) propanoic acid and 10% d_2-(2S,3S)-2-amino-2,3-dideuterio-3-(3,4-dihydroxyphenyl) propanoic acid (data on file, Teva Pharmaceutical Industries).

Studies in rodents confirmed that the intended deuteration in SD-1077 enhances the striatal DA output as measured by microdialysis more effectively than L-DOPA without changes of the peripheral PK and without significant increase of central DA peak concentrations [18, 19]. Observation of a decreased DOPAC/DA ratio confirmed that slower breakdown by MAO contributed to lower DA turnover. In rodent models of Parkinson's disease d3-(2S)-2-amino-2,3,3-trideuterio-3-(3,4-dihydroxyphenyl) propanoic acid was more potent at reducing motor behavior deficits than L-DOPA [18–20]. Approximately 60% of the traditional L-DOPA dose was equipotent as defined by the dose that produced 50% of the maximally observed motor performance and induced less dyskinesia in chronic treatment [20]. In 6-OHDA-lesioned rats the observed motor performance showed similar magnitude to that of L-DOPA in combination with the **MAO-B** inhibitor **selegiline**, an effect attributed to decreased metabolism of L-DOPA by MAO-B [18].

We compared plasma pharmacokinetics after single-dose oral administration of 150 mg SD-1077 (corresponding to 60% of a confirmed safe L-DOPA dose of 250 mg) [21] or L-DOPA, both coadministered with 37.5 mg **carbidopa** (CD) under fasted conditions in healthy subjects. We evaluated the potential for attenuated dopamine metabolism or more profound shifts in the metabolic pathway by comparing the peripheral pharmacokinetics and urinary excretion of metabolites following SD-1077/CD and L-DOPA/CD administration. Plasma and urine PK data were used to construct a mechanistic population PK model to simulate PK of SD-1077 and metabolites relative to L-DOPA.

Methods

Study drug

SD-1077 was manufactured by Chiracon GmbH (Luckenwalde, Germany) and processed by Teva Branded Pharmaceutical Products R&D, Inc. (Frazer, PA, USA). L-DOPA was purchased from Ajinomoto Co., Inc (Kawasaki, Japan). The investigational product, an aqueous oral solution of 250 mL containing 150 mg SD-1077 and 500 mg ascorbic acid as pH modifier to increase active pharmaceutical ingredient solubility, and the reference product, an aqueous oral solution of 250 mL containing 150 mg L-DOPA and 500 mg ascorbic acid, were prepared at the pharmacy of PRA (Zuidlaren, the Netherlands). Lodosyn tablets containing 25 mg CD were purchased from Valeant Pharmaceuticals (Bridgewater, NJ USA).

Subjects and study design

This study was conducted at PRA (Zuidlaren, the Netherlands) in full accordance with the International Conference on Harmonization Good Clinical Practice Consolidated Guideline (E6) consistent with the principles that have their origin in the Declaration of Helsinki. Before the study was initiated, the protocol was submitted to the Independent Ethics Committee of the Foundation *Evaluation of Ethics in Biomedical Research* (Assen, the Netherlands). Subjects provided informed consent.

This was a single-centre, double-blind, single-dose, two-treatment period, crossover study to evaluate the PK and safety profiles of SD-1077 and L-DOPA, each in combination with an oral dose of CD in healthy subjects. A total of 16 healthy subjects, age 25–40 years (BMI ≥18.5 and ≤30.0 kg m^{-2}), meeting inclusion and exclusion criteria were randomized to one of two treatment sequences.

The study consisted of a screening visit within 28 days prior to first dosing followed by two treatment periods consisting of a 3-day inpatient stay separated by a minimum 7-day washout period, and an end of study assessment visit (approximately 7 days after completion of period 2 assessments). During the first treatment period, subjects received a single dose of 37.5 mg CD (1½ × 25 mg tablets with 200 mL water) 30 min prior to receiving either investigational or reference product. Subjects with marked nausea post treatment in period 1 were given prophylaxis with **domperidone** (20 mg, oral) at the same time of CD administration in period 2. Blood samples were collected prior to CD dosing, prior to SD-1077 or L-DOPA dosing, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14 and 24 h post SD-1077 or L-DOPA dosing. Urine samples were collected at the following intervals: prior to dosing with CD from –2 to 0 h, and then at 0–2, 2–4, 4–8 and 8–24 h after administration of SD-1077 or L-DOPA.

Quantification of drug and metabolite concentrations in plasma and urine

The plasma and urine concentrations of SD-1077, L-DOPA, their metabolites (DA, 3-MT, 3-OMD, DOPAC and HVA) and CD were obtained using validated liquid chromatography with tandem mass spectrometry methods (Model 6500 tandem mass spectrometer, AB Sciex, Concord, Canada). 3-MT was not quantified in urine considering the low abundance and the required lower limit of quantitation. During bioanalytical analysis, two ion channels were monitored simultaneously for each analyte, with the exception of CD, to measure the deuterated form and the nondeuterated form. When SD-1077 was administered, the total concentration (endogenous + exogenous) of L-DOPA or metabolite was quantified by taking the sum of the deuterated and nondeuterated moieties. Following L-DOPA administration the total concentration of L-DOPA and metabolites equates the nondeuterated concentration. Low apparent concentrations of some analytes with a mass corresponding to the expected deuterated form, detected following L-DOPA administration, were discounted as they were thought to be due to naturally occurring heavy isotopes.

Pharmacokinetic evaluation

Primary parameters to evaluate the comparative plasma PK following administration of SD-1077/CD and L-DOPA/CD were maximum observed plasma drug concentration (C_{max}) and area under the plasma concentration–time curve from time 0 to infinity (AUC_{0-inf}). Additionally, the following PK parameters were calculated: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{0-t}), percentage of AUC_{0-inf} extrapolated ($\%AUC_{extrap}$), time to C_{max} (t_{max}), terminal elimination half-life ($t_{½}$). Apparent total body clearance and apparent volume of distribution during the terminal phase were calculated for SD-1077 only based on concentration of the deuterated moiety. Plasma PK parameters were calculated using Phoenix WinNonlin version 6.3 (Pharsight Corporation, Mountain View, USA) with noncompartmental analysis. Quantification limit for L-DOPA and SD-1077 was 5.0 ng ml^{-1} and 100 ng ml^{-1}, respectively.

The amount of SD-1077, L-DOPA, CD and metabolites excreted in urine was assessed for each collection interval and total (0–24 h), where feasible, along with urine creatinine levels at each sampling point, and with serum creatinine levels prior to dosing.

Statistical analysis

Statistical comparisons and descriptive statistics were generated using SAS® Version 9.4 (SAS Institute Inc. Cary, NC USA). Statistical comparison of PK parameters were based on natural log transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ data between treatments (Test vs. Reference) was carried out using a parametric analysis of variance (ANOVA) model with terms for sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. The model-based estimated treatment means (LSmeans) and treatment difference (Test – Reference) in LSmeans and the associated 90% CI estimated from the ANOVA model on the log scale was back-transformed to original scale by exponentiation to obtain the estimated treatment geometric means and ratio (Test/Reference) of geometric means between treatments and the 90% CI for this ratio.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [22], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [23].

Results

Demographics

The mean age of the subjects was 28 years (range: 25–33 years), mean weight was 68 kg (range: 52–86 kg), and mean BMI was 22.1 kg m^{-2} (range: 19.6–26.0 kg m^{-2}). Of the 16 subjects randomized, seven (44%) were male and nine (56%) were female. The majority of subjects were Caucasian (14, 88%), one (6%) was Black and one (6%) was of *other* race. Two (13%) subjects were of Hispanic or Latino ethnicity.

Plasma pharmacokinetics

Mean predose plasma concentrations of endogenous L-DOPA were below limit of quantitation. Following administration, SD-1077 and L-DOPA were rapidly absorbed and displayed comparable mean plasma concentration-time profiles as shown in Figure 2. Plasma PK parameters of SD-1077, L-DOPA, metabolites and CD are presented in Table 1. Systemic exposures to SD-1077 and L-DOPA were comparable as reflected by mean AUC, C_{max} and $t_{½}$. Systemic

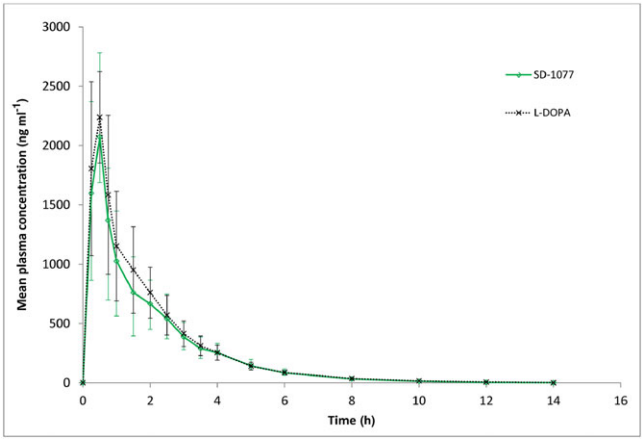

Figure 2

Mean (± standard deviation) SD-1077 and L-DOPA plasma concentration *vs*. time. Abbreviations include L-DOPA L-3,4-dihydroxyphenylalanine

exposure to CD was generally comparable between SD-1077/CD and L-DOPA/CD. As shown in Table 2, the confidence intervals of the geometric mean ratios between SD-1077 and L-DOPA for AUC_{0-t}, and AUC_{0-inf} were within the range of 80–125%. The geometric mean ratio for C_{max} showed a higher variability with a lower limit of 75.9%.

The mean DA plasma concentrations *vs*. time are displayed in Figure 3. Peak DA concentrations were reached rapidly for both treatments. DA concentrations were about three orders of magnitude lower than parent drug for both treatments. The mean terminal half-life was comparable for both treatments. Systemic exposure to DA was significantly higher after SD-1077/CD compared to that after L-DOPA/CD, with geometric means ratios (90% CI) of 1.8 (1.45–2.24; $P = 0.0005$) and 2.06 (1.68–2.52; $P < 0.0001$) for C_{max} and AUC_{0-t}, respectively. The individual ratio of DA/SD –1077 was inversely correlated to the individual CD concentration at the first PK time point of 0.25 h post dose but not at subsequent time points (Figure 4). No significant correlation was found for DA/L-DOPA to CD at 0.25 h post dose.

The mean $t_{½}$ of DOPAC was comparable following SD-1077/CD (0.94 h) and L-DOPA/CD (1.1 h) but systemic exposure to DOPAC was slightly lower following SD-1077/CD compared to L-DOPA/CD, with geometric LSmeans ratios (90% CI) of 0.83 (0.72, 0.95; $P = 0.0357$), 0.87 (0.76, 0.99; $P = 0.0776$), and 0.89 (0.78, 1.01; $P = 0.1146$) for C_{max}, AUC_{0-t}, and AUC_{0-inf}, respectively. The median metabolic ratio of DOPAC/DA in plasma *vs*. time is displayed in Figure 5. Mean DOPAC concentration vs. time is displayed in Supplemental Figure S1. This ratio was 1.4–2.6-fold higher following L-DOPA/CD compared to SD-1077/CD at the time points with measurable plasma concentrations of DA and DOPAC. Systemic exposure to HVA was generally comparable following both treatments (Figure S2).

For the first 2.5 h following drug administration of SD-1077/CD, mean 3-OMD plasma concentrations were comparable to those following L-DOPA/CD, and were higher thereafter (mean concentration vs. time is displayed in Figure 6). Peak concentrations were reached relatively slowly and declined slowly. After 24 h, plasma concentrations were still 52% and 42% of the peak concentration for SD-1077/CD and L-DOPA/CD, respectively. Systemic exposure to 3-OMD was higher following SD-1077/CD compared to that of L-DOPA/CD, with geometric LS means ratios (90% CI) of 1.19 (1.15, 1.23; $P < 0.0001$) and 1.31 (1.27, 1.36; $P < 0.0001$) for C_{max} and AUC_{0-t}, respectively. The terminal elimination phase was not achieved at the last sampling

Table 1

Mean (standard deviation) plasma pharmacokinetic parameters

Treatment	Analyte	C_{max} [ng ml^{-1}]	t_{max}[a] [h]	AUC_{0-t} [ng h ml^{-1}]	AUC_{0-inf} [ng h ml^{-1}]	$t_{1/2}$ [h]
L-DOPA/CD	L-DOPA	2479 (464)	0.50 (0.25, 0.75)	3920 (751)	3935 (751)	1.53 (0.13)
	CD	148 (54)	2.50 (1.25, 4.03)	772 (243)	779 (243)	3.44 (1.12)
	DA	1.81 (1.22)	0.25 (0.25, 0.75)	2.31 (1.57)	4.16 (2.02)	6.04 (2.96)
	DOPAC	222 (73)	0.50 (0.49, 0.75)	260 (80)	279 (82)	1.06 (0.16)
	HVA	273 (98)	0.75 (0.50, 1.00)	902 (289)	NA	NA
	3-OMD	1029 (219)	5.00 (3.52, 6.00)	16 853 (3285)	NA	NA
	3-MT	0.6 (0.33)	0.25 (0.25, 0.75)	0.48 (0.33)	0.78 (0.46)	0.83 (0.58)
SD-1077/CD	SD-1077 + L-DOPA	2252 (730)	0.50 (0.25, 0.75)	3526 (843)	3543 (843)	1.40 (0.12)
	CD	142 (50)	2.50 (0.75, 4.00)	725 (228)	734 (229)	3.06 (1.32)
	DA-d3 + DA	3.30 (2.24)	0.50 (0.25, 0.50)	4.61 (3.03)	5.91 (3.55)	5.78 (2.88)
	DOPAC-d2 + DOPAC	181 (61)	0.50 (0.52, 0.75)	221 (61)	240 (64)	0.94 (0.18)
	HVA-d2 + HVA	246 (64)	0.75 (0.5, 1.5)	842 (198)	NA	NA
	3-OMD-d3 + 3-OMD	1237 (326)	6.00 (5.00, 6.00)	22 276 (5533)	NA	NA
	3-MT-d3 + 3-MT	0.78 (0.42)	0.25 (0.25, 0.5)	0.69 (0.36)	0.98 (0.34)	1.05 (0.58)

[a]Median (min, max)

Abbreviations include NA, not applicable; 3-MT, 3-methoxytyramine; 3-MT-d3, deuterated 3-methoxytyramine; 3-OMD, 3-O-methyldopa; 3-OMD-d3, deuterated 3-OMD; CD, carbidopa; DA, dopamine; DA-d3, deuterated dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; DOPAC-d2, deuterated DOPAC; HVA, homovanillic acid; HVA-d2, deuterated HVA; L-DOPA, L-3,4-dihydroxyphenylalanine

Table 2

Statistical comparison of pharmacokinetics

Parameter	Geometric LS Mean L-DOPA	Geometric LS Mean SD-1077	Geometric LS mean ratio SD-1077/L-DOPA [%]	90% CI of geometric LS mean ratio SD-1077/L-DOPA [%]
C_{max}	2437.02	2155.21	88.4	75.9, 103.1
AUC_{0-t}	3857.29	3453.20	89.5	84.1, 95.3
AUC_{0-inf}	3872.85	3470.79	89.6	84.2, 95.4

Abbreviations include CI, confidence interval; LS, least squares; L-DOPA, L-3,4-dihydroxyphenylalanine

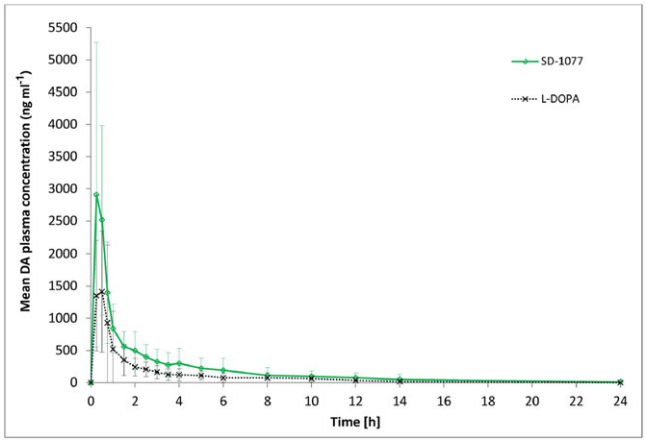

Figure 3

Mean DA plasma concentration *vs.* time. DA dopamine

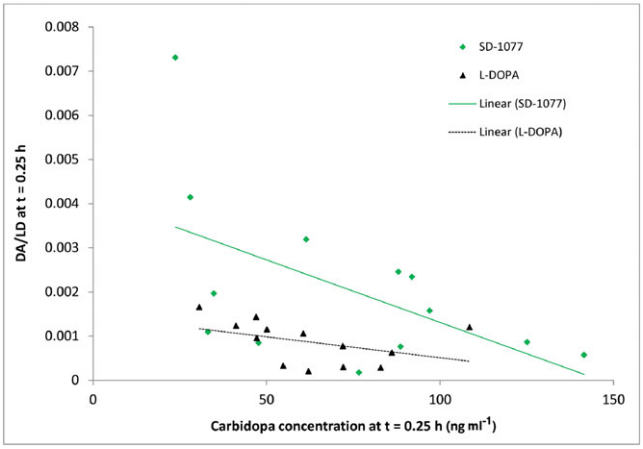

Figure 4

Ratio of DA/L-DOPA plasma concentrations *vs.* CD concentration at 0.25 h postdose DA/L-DOPA is inversely correlated with CD at. 25 h for SD-1077 (green line, r^2 = –0.55 P = 0.0502) but not L-DOPA (grey line, r^2 = –0.41, P = 0.1569). CD carbidopa; DA dopamine; L-DOPA L-3,4-dihydroxyphenylalanine; t time

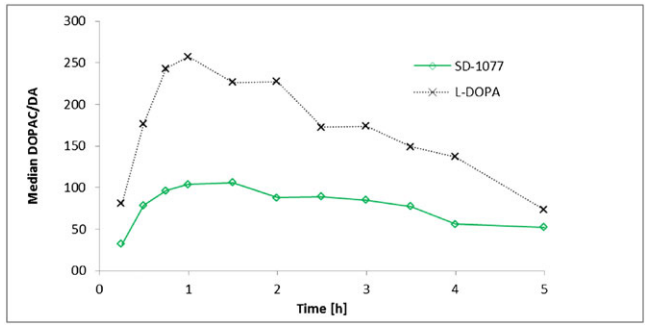

Figure 5

Median ratio of DOPAC/DA plasma concentrations *vs.* time. DA dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid

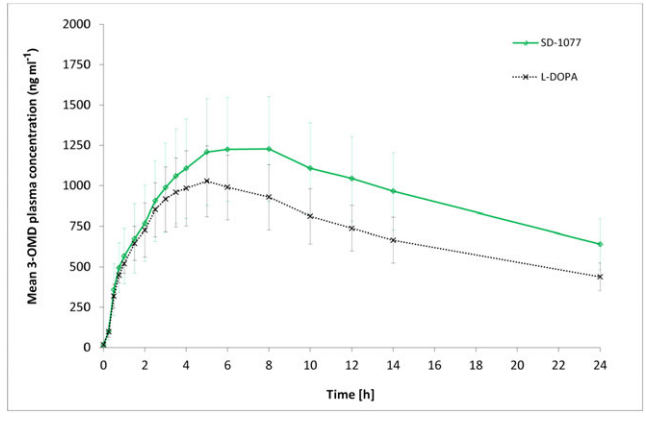

Figure 6

Mean 3-OMD plasma concentration *vs.* time. 3-OMD, 3-O-methyldopa

time point, and AUC_{0-inf} and $t_{½}$ could not be determined. Peak 3-MT plasma concentrations occurred rapidly (Figure 7). Systemic exposure to 3-MT was higher after administration of SD-1077/CD compared to that following L-DOPA/CD, with

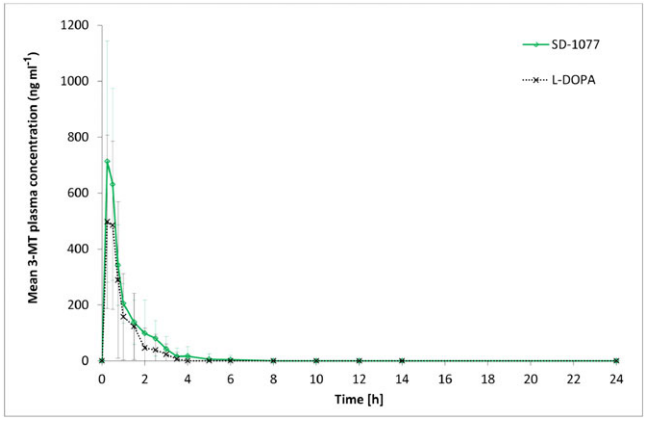

Figure 7

Mean 3-MT plasma concentration *vs.* time. 3-MT, 3-methoxytyramine

geometric LS means ratios (90% CI) of 1.33 (1.14, 1.56; $P = 0.0077$) and 1.66 (1.42, 1.93; $P < 0.0001$) for C_{max} and AUC_{0-t}, respectively.

Urine pharmacokinetics

The total amount of drug and metabolites excreted in urine was determined based on measured urine concentrations of the nondeuterated + deuterated analytes for SD-1077/CD and the nondeuterated analytes for L-DOPA/CD. No L-DOPA and carbidopa was present in urine before administration of either SD-1077/CD or L-DOPA/CD but HVA, DOPAC, DA and 3-OMD were present in descending order.

Results of statistical comparison of the total amounts of unchanged drug and metabolites excreted in urine per time interval are displayed in Table 3. There were no significant differences between treatments for the total amounts of L-DOPA, CD, HVA and DOPAC excreted in urine. The highest amount of deuterated or nondeuterated L-DOPA was excreted in the interval between 0 and 2 h postdose, during which the amount excreted was comparable for both treatments as during all other collection intervals. Excretion of the unchanged deuterated and nondeuterated L-DOPA was almost completed at 8 h post dose.

The total amount of DA excreted in the 24-h sampling time following SD-1077/CD was significantly higher as

Table 3

Statistical comparison of amount analyte (μg) excreted in urine by time interval

Analytes	Time (h)	LS mean SD-1077 (T)	LS mean L-DOPA (R)	LS means difference (T – R)	90% CI	*P*-value
L-DOPA	0–2	5864.43	5935.16	–70.73	(–796.54, 655.07)	0.8622
	2–4	2832.51	2980.20	–147.69	(–1062.45, 767.06)	0.7758
	4–8	972.75	1190.91	–218.16	(–655.35, 219.04)	0.3894
	8–24	170.11	248.56	–78.45	(–218.12, 61.23)	0.3348
	0–24	9658.39	9376.23	282.16	(–1094.66, 1658.97)	0.7198
DOPAC	0–2	4317.60	4677.44	–359.84	(–1919.57, 1199.89)	0.6847
	2–4	1729.35	2030.72	–301.37	(–950.64, 347.90)	0.4199
	4–8	599.62	847.12	–247.5	(–552.86, 57.87)	0.1735
	8–24	1091.80	1017.54	74.26	(–173.05, 321.58)	0.6005
	0–24	7616.84	8175.51	–558.67	(–2184.86, 1067.53)	0.5498
3-OMD	0–2	600.87	453.29	147.58	(17.54, 277.61)	0.0667
	2–4	1107.75	1041.74	66.01	(–38.88, 170.90)	0.2806
	4–8	1742.18	2182.15	–439.97	(–843.08, –36.86)	0.0758
	8–24	4126.46	6163.82	–2037.36	(–2961.94, –1112.8)	0.0022
	0–24	7533.74	9816.17	–2282.43	(–3169.77, –1395.08)	0.0007
DA	0–2	2159.20	1013.65	1145.55	(265.97, 2025.14)	0.0399
	2–4	567.65	390.58	177.07	(–57.06, 411.19)	0.2004
	4–8	314.59	246.16	68.43	(–71.11, 207.98)	0.3973
	8–24	462.13	368.06	94.07	(–48.15, 236.29)	0.2599
	0–24	3463.76	1936.25	1527.51	(656.50, 2398.53)	0.0093
HVA	0–2	8569.29	7824.68	744.61	(–1661.06, 3150.27)	0.5871
	2–4	7025.89	7379.32	–353.43	(–1581.84, 874.99)	0.6134
	4–8	3796.15	4377.75	–581.6	(–1597.85, 434.65)	0.3261
	8–24	5859.09	5723.64	135.45	(–813.43, 1084.34)	0.8024
	0–24	24720.01	24607.13	112.88	(–2375.90, 2601.66)	0.9365

P-values are calculated from fitting ANOVA model with parameters for sequence, treatment, and period as fixed effects and subjects within sequence as random effect using SAS PROC MIXED

Abbreviations include 3-OMD, 3-O-methyldopa; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; L-DOPA, L-3,4-dihydroxyphenylalanine, LS means least square means; 90% CI, 90% confidence interval

compared to L-DOPA/CD (P = 0.0093) and the amount was consistently higher in each collection interval for the SD-1077/CD treatment group. For the metabolite, 3-OMD, the total amount excreted in the 24-h sampling time was significantly higher following L-DOPA/CD compared to SD-1077/CD (P = 0.0007). However, the difference was only visible between 8 and 24 h and the amounts excreted between 0–2 h, 2–4 h and 4–8 h were comparable between treatments (Table 3).

Safety and tolerability

Twelve (75%) subjects experienced at least one adverse event (AE) during the study (Table 4). Incidence of subjects with at least one AE was comparable for both SD-1077/CD (eight, 57% subjects) and L-DOPA/CD (seven, 47% subjects). There were no serious or severe AEs reported during the study. Three subjects (one subject on SD-1077/CD and two on L-DOPA/CD) withdrew from the study in Period 1 due to vomiting within 4 h of study drug administration. Treatment-emergent AEs of moderate intensity were nausea and vomiting, observed in the first period for both treatments and successfully mitigated with domperidone prophylaxis (20 mg oral at the same time of carbidopa administration) in Period 2. In the first treatment period, six subjects receiving SD-1077 (sequence AB) and five receiving L-DOPA (sequence BA) were treated with domperidone. The subjects who continued the study (five in sequence AB and three in sequence BA) received domperidone prophylaxes in the second period. No domperidone treatment was required for five subjects (two in sequence AB and three in sequence BA). These events were considered treatment-related and had comparable incidence between treatments (43% *vs.* 33% for SD-1077/CD and L-DOPA/CD, respectively) and corresponded with peak peripheral DA concentration. All other AEs were of mild intensity. Reports of hot flush and postural dizziness were unique to SD-1077/CD treatment and corresponded to the peak peripheral concentration of free DA.

There were no clinically meaningful trends in mean changes from baseline for blood pressure, respiratory rate or body temperature. Similarly, there were no clinically meaningful trends in clinical laboratory variable or echocardiography. A nonclinically significant increase in pulse rate was observed after both treatments.

Discussion

The present study confirmed that selective deuteration in SD-1077 attenuates the metabolic degradation of the deuterated dopamine in plasma relative to L-DOPA in healthy subjects coadministered CD. Consistent with the location of the deuterium atoms, greater exposure to DA was accompanied by a decreased ratio of DOPAC/DA following SD-1077 compared to L-DOPA confirming a reduced rate of deamination of DA by MAO. A higher stability of deuterated DA against metabolic breakdown by MAO is also substantiated by the higher amount excreted in urine. The effect of

Table 4

Treatment-emergent adverse events by system organ class, preferred term and treatment

System organ class MedDRA 10.1 preferred term, n (%)	SD-1077/CD (n = 14)	L-DOPA/CD (n = 15)	Overall (n = 16)
Gastrointestinal disorders	6 (43)	7 (47)	11 (69)
Nausea	6 (43)	7 (47)	11 (69)
Vomiting	1 (7)	2 (13)	3 (19)
Abdominal distension	1 (7)	0 (0)	1 (6)
General disorders/administration site conditions	2 (14)	0 (0)	2 (13)
Hunger	1 (7)	0 (0)	1 (6)
Pyrexia	1 (7)	0 (0)	1 (6)
Infections/infestations	1 (7)	0 (0)	1 (6)
Nasopharyngitis	1 (7)	0 (0)	1 (6)
Nervous system disorders	5 (36)	2 (13)	6 (38)
Headache	2 (14)	1 (7)	3 (19)
Dizziness	2 (14)	1 (7)	2 (13)
Dizziness postural	1 (7)	0 (0)	1 (6)
Somnolence	1 (7)	0 (0)	1 (6)
Vascular disorders	3 (21)	0 (0)	3 (19)
Hot flush	3 (21)	0 (0)	3 (19)

Abbreviations include CD, carbidopa; L-DOPA, L-3,4-dihydroxyphenylalanine

selective deuteration in SD-1077 on the metabolic rate of DA following SD-1077 was not reflected in its terminal half-life, probably due to its elimination half-life of a few minutes in plasma as determined after intravenous administration by Onasch *et al*. [24]. Due to the rapid elimination the terminal decline of the DA plasma concentration is probably determined by the absorption and its formation rate. The formation of DA by decarboxylation of the precursor does not involve the deuterated positions in SD-1077 and is therefore not impaired at comparable carbidopa levels. The comparable peripheral exposure to and urinary excretion of CD in both treatment groups confirms that DDC was inhibited equally and did not bias the plasma concentrations of the delivered treatments or their relevant metabolites. The early appearance of peak DA concentrations relative to the precursors, suggest that a part of DA is formed extravascularly. A deuterium effect on absorption is not to be expected because no difference in the binding of regular DA and deuterated DA to the DA transporter was found *in vitro* [18]. The effect on deuterated DA turnover in the periphery is supportive by experiments in rats [20] where a lower equipotent dose was demonstrated. The magnitude of the effect in the human brain cannot be readily predicted from peripheral findings because MAO distribution, release, reuptake and storage influence DA turnover.

The attenuated breakdown of deuterated DA by MAO has the potential to provide a Parkinson's disease patient steadied central dopamine levels that allow less frequent daily intake and avoidance of motor fluctuations. The concentrations time curves of striatal DA observed following intraperitoneal administration to healthy rats, d3-(2S)-2-amino-2,3,3-trideuterio-3-(3,4-dihydroxyphenyl) propanoic acid show a prolonged increase without significant higher peak levels as compared to L-DOPA [19]. The fact that an equipotent dose of d3-(2S)-2-amino-2,3,3-trideuterio-3-(3,4-dihydroxyphenyl) propanoic acid induced fewer and not more dyskinesias at the same dose than L-DOPA in the 6-OHDA rodent model of Parkinson's disease [20] supports the potential of the drug to reduce fluctuations. To confirm central effects of the drug in humans, the efficacy and safety of SD-1077 needs to be investigated in patients. Additionally, a lower exposure to the transient toxic metabolites DOPAL [25] and a lower catecholamine load in the brain could be expected, both with the potential to reduce neurotoxic effects [26]. The peripheral effects of higher DA plasma peak levels after SD-1077 are deemed to be acceptable in Parkinson's disease patients considering reported exposure to DA in this population (e.g. [27]).

The selective deuteration in SD-1077 did not significantly affect the exposure to the parent drug. Considering that the study was not powered to demonstrate bioequivalence, the systemic exposures to SD-1077 and L-DOPA were comparable, consistent with the findings that deuterium substitution did not affect the peripheral PK after intraperitoneal administration in rats [20]. This finding is also reflected by similar amounts of unchanged drug excreted to urine following SD-1077/CD and L-DOPA/CD and consistent with the lack of the impacted deuterated positions in the decarboxylase reaction forming DA from the parent. The bond cleavage involved in the DDC-dependent formation of DA is remote from the C-D bonds in SD-1077 [28], consistent with the lack of primary kinetic isotope effect on SD-1077 pharmacokinetics. In contrast both deamination of DA by MAO and hydroxylation by DBH involve the cleavage of C-D [29, 30].

In the therapy of Parkinson's disease with L-DOPA/CD immediate release (IR) formulations, at least 70–100 mg of carbidopa per day is being provided. In the present study we administered the standard 4:1 ratio of L-DOPA/CD as it is used for patients with a need of 300–400 mg (3–4 doses) L-DOPA per day. CD was administered 30 min before administration of the oral solution containing SD-1077 or L-DOPA to ensure DDC inhibition comparable to that of commercially available L-DOPA/CD formulations. The peak concentration of CD was reached 1.5 h after peak concentrations of L-DOPA. This delay is similar to that observed after administration of a commercially available L-DOPA/CD IR formulation to healthy subjects [31].

The robust representation of L-DOPA and SD-1077 metabolite products of decarboxylation (DA, DOPAC and HVA) shows that DDC is not fully inhibited. An impact of individual carbidopa concentrations on the DA/L-DOPA ratios was only visible at 0.25 h post where the ratio was inversely correlated to the individual CD concentration. The finding that the correlation was steeper for SD-1077 as compared to L-DOPA indicates that a suboptimal DDC inhibition has a higher impact on SD-1077 because of the attenuated degradation of the peripherally formed deuterated DA. The slower absorption of CD compared to L-DOPA and SD-1077 could explain that DDC inhibition is less efficient at this time point. Increase of CD beyond the standard ratio has been shown to increase L-DOPA availability [32]. However, CD irreversibly binds to and permanently deactivates pyridoxal 5′-phosphate and PLP-dependent enzymes and depletes PLP reserve pools [33] and experiences with higher CD doses are limited. The change of L-DOPA/CD plasma levels over time needs to be considered if improvement of DDC inhibition is targeted.

The slightly higher exposure to 3-MT following SD-1077/CD *vs*. L-DOPA/CD is expected based on the higher DA levels and because 3-MT is metabolized by MAO similar to DA including the same deuterated position. Malmlöf *et al*. (2015) [18] showed in an animal model of Parkinson's disease that the higher exposure of 3-MT following administration of triple-deuterated d3-L-DOPA is less than compared to that observed after MAO-B inhibitor selegiline and L-DOPA although selegiline pretreatment did not potentiate the effect of d3-L-DOPA on DA output. The expected increase of 3-MT is less than after administration of regular L-DOPA at concomitant MAO inhibition.

The slightly higher exposure to 3-OMD in plasma following SD-1077/CD *vs*. L-DOPA/CD may reflect slower metabolism of the deuterated metabolite. 3-OMD is metabolized to 4-hydroxy-3-methoxyphenylpyruvic acid (HMPPA) and vanillactic acid. The formation of HMPPA is a reversible reaction metabolized by **tyrosine aminotransferase**, which involves the cleavage of a C-D bond required for a primary isotope effect. This enzyme has also been shown to metabolize a small proportion of L-DOPA to form 3,4-dihydroxyphenylpyruvic acid [34]. The fact that differences in 3-OMD levels between treatments appeared after L-DOPA and SD-1077 concentrations decreased below 3-OMD concentrations might indicate a competition of 3-OMD and L-DOPA or SD-1077 as substrate for tyrosine aminotransferase. In urine, excretion of 3-OMD is comparable between treatments

until excretion of the parent drug is completed and higher thereafter in the L-DOPA/CD group. Two processes might be impacting these results, 3-OMD reuptake via amino acid transporter and reformation of 3-OMD from HMPPA. The d2–3-OMD reformed from HMPPA would have had one deuterium replaced by hydrogen and would not be detected by mass spectrometry because of the different mass to d3–3-OMD. Thus, the available data are not sufficient to draw a conclusion. Non-clinical studies suggested that 3-OMD competes with L-DOPA for the blood–brain barrier transporter system [35]. Observed differences in exposure to 3-OMD between SD-1077 and L-DOPA are small but the addition of a COMT inhibitor could further improve the clinical profile of SD-1077.

Overall, single-dose administration of 150 mg SD-1077/37.5 mg CD in healthy volunteers was well tolerated and comparable with that of single-dose administration of 150 mg L-DOPA/37.5 mg CD. The observed safety profile was expected based on the pharmacology of L-DOPA and CD. The occurrence of nausea, vomiting, headache and hot flush appeared to coincide with the mean peak free DA concentration. Hot flush and dizziness was reported after SD-1077/CD only but are a known side effect of L-DOPA/CD [36]. The incidence of nausea and vomiting was higher than previously reported with IR tablets of **Sinemet** [33], possibly reflecting the faster absorption from the administered oral solutions. While nausea and vomiting are an expected occurrence in levodopa naïve subjects, they are not expected to be dose-limiting in a multiple dose setting in patients, as tolerance invariably develops. Flushing and dizziness can reflect sympathomimetic conversion centrally and need to be monitored carefully in subsequent clinical trials.

In conclusion, the results of the present study give the first clinical evidence in human showing that selective deuteration in the α and β positions of the L-DOPA side chain causes a reduction of the metabolic breakdown of DA by MAO due to the intended deuterium isotope effect on this reaction. We demonstrated comparable peripheral PK and safety of a single oral dose of SD-1077/CD compared to L-DOPA/CD in healthy subjects. Additional quantitative changes in metabolite exposures from SD-1077 relative to L-DOPA were all readily explained by the expected deuterium kinetic isotope effects without indication of a major shift or switch in the main metabolic pathway and did not raise concern with regard to safety. The study results support SD-1077 potential to prolong the availability of DA in the brain in comparison to conventional L-DOPA with vastly less impact on peripheral PK. The full potential for SD-1077 might be realized with further approaches to increase its peripheral availability.

Contributors

F.S. created the study design, provided data interpretation and wrote the first draft of the manuscript. L.E. was involved in study conception, safety data evaluation, data interpretation and manuscript review. H.B. and M.M. conducted statistical analyses and reviewed the manuscript. I.D.G. was Project Physician, involved in the safety reviews and interpretation of study results and in manuscript review and revisions. M.B., J.-M.S. and S.P. provided data interpretation and manuscript review. O.C.B. and O.S. provided study conception, data interpretation and manuscript review. P.S.L. provided data interpretation and manuscript writing. S.G. and M.L. provided PopPK analysis design and execution and manuscript review. W.T. provided PK data evaluation and manuscript review. M.V. was the study principal investigator and provided manuscript review.

Competing Interests

F.S., L.E., H.B., O.C.B., I.D.G., P.S.L., M.L., M.M., J.-M.S., W. G.T. and O.S. are employees of Teva Pharmaceutical Industries, who are sponsoring the clinical development of SD-1077 for the treatment of Parkinson's disease. S.P. was employed by Teva at the time of the study but is now affiliated with Massachusetts General Hospital Harvard University (Boston MA), M.B. was employed by Teva at the time of the study but is now affiliated with Prana Biotechnologies, S.G. is CEO of PopPharm, Israel and M.V. is an employee of PRA Health Sciences - Early Development Services (Groningen, the Netherlands).

All studies described in this report were funded by Teva Pharmaceutical Industries, Ltd.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13702/suppinfo.

Figure S1 Mean 3,4-dihydroxyphenylacetic acid plasma concentration *vs*. time

Figure S2 Mean homovanillic acid plasma concentration *vs*. time