1. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
BIAL – Portela & C[a] S.A.</td><td rowspan="3">Individual Study Table referring to Part ..... of Dossier

Volume:</td><td rowspan="3">(For authorities use only)</td></tr>
<tr><td>Name of finished product:
To be determined</td></tr>
<tr><td>Name of active ingredient:
(Opicapone) BIA 9-1067</td></tr>
<tr><td colspan="3">Title:
A double-blind, randomised, Placebo-controlled, cross-over study to investigate the tolerability and effect of three single-dose regimens of BIA 9-1067 on the levodopa pharmacokinetics, motor response, and erythrocyte soluble catechol-O-methyltransferase activity in Parkinson’s Disease patients concomitantly treated with levodopa/dopa-decarboxylase inhibitor</td></tr>
<tr><td colspan="3">Clinical Study Sites, Principal Investigators and Sub-Investigators:
Centre 1:
Department of Neurology, Spitalul Clinic Colentina, Bucharest, Romania.
Principal Investigator: Prof. Dr. Marina Ticmeanu.
Centre 2:
Department of Neurology, Hospital de Santa Maria, Lisbon, Portugal.
Principal Investigator: Prof. Dr. Joaquim Ferreira.
Centre 3:
Department of Neurology, Hospital of the Department of Medical Care of Ministry of Internal Affairs of Ukraine, Kyiv, Neurological center, Ukraine.
Principal Investigator: Dr. Larysa Bezukh.</td></tr>
<tr><td colspan="3">Publication reference:
Not published, at the time of this report</td></tr>
<tr><td colspan="2">Study period:
Date of first screening: 09APR2009
Date of last visit: 25FEB2010</td><td>Clinical phase:
Phase II / Therapeutic Exploratory</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To investigate the effect of three single oral doses of BIA 9-1067 (25 mg, 50 mg and 100 mg) on the levodopa pharmacokinetics when administered in combination with immediate release 100 mg/25 mg levodopa/carbidopa or 100 mg/25 mg levodopa/benserazide in Parkinson’s Disease (PD) patients.
Secondary:
To investigate the tolerability and safety of three single oral doses of BIA 9-1067 (25 mg, 50 mg and 100 mg) when co-administered with immediate release 100 mg/25 mg levodopa/carbidopa or 100 mg/25 mg levodopa/benserazide in PD patients.
To investigate the effect of three single oral doses of BIA 9-1067 (25 mg, 50 mg and 100 mg) on the motor response to immediate release 100 mg/25 mg levodopa/carbidopa or 100 mg/25 mg levodopa/benserazide in PD patients with end-of-dose deterioration.
To investigate the effect of three single oral doses of BIA 9-1067 (25 mg, 50 mg and 100 mg) on the erythrocyte soluble catechol-O-methyltransferase (S-COMT) activity when co-administered with immediate release 100 mg/25 mg levodopa/carbidopa or 100 mg/25 mg</td></tr>
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levodopa/benserazide in PD patients.
To investigate the pharmacokinetics of three single oral doses of BIA 9-1067 (25 mg, 50 mg and 100 mg) when co-administered with immediate release 100 mg/25 mg levodopa/carbidopa or 100 mg/25 mg levodopa/benserazide in PD patients.

Study design and methodology:
This was a three-centre, double-blind, randomised, Placebo-controlled, crossover study with four consecutive single-dose treatment periods in PD patients treated with immediate release 100 mg/25 mg levodopa/carbidopa or 100 mg/25 mg levodopa/benserazide. The washout period between doses was to be at least 10 days. According to randomisation, subjects were to receive, in a double-blind manner, 25 mg, 50 mg, 100 mg BIA 9-1067 and Placebo at 4 separate treatment periods. On each period, the BIA 9-1067/Placebo capsules were to be co-administered with the morning dose of 100 mg/25 mg levodopa/carbidopa (1 tablet of Sinemet® 25/100) or 100 mg/25 mg levodopa/benserazide (1 tablet of Madopar®/Restex® 125) on Day 3.

Sample size (planned and analyzed):
Planned: 12 subjects were to be enrolled. Analysed: 10 subjects were enrolled and completed 3 treatment periods. Nine (9) subjects completed all 4 treatment periods. One (1) subject withdrew the consent due to personal reasons. The mean (±SD) age, height and weight were 58.40±10.24 (range: 42-70) years, 1.69±0.14 (1.52-1.95) m, 71.5±15.06 (50-100) kg, respectively.

Diagnosis and main selection criteria:
Male or female of non-childbearing potential (by reason of surgery or postmenopausal) aged between 30 and 75 years, inclusive; a diagnosis of PD according to the UK PDS Brain Bank diagnostic criteria (bradykinesia and at least one of the following: muscular rigidity, rest tremor and postural instability); predictable signs of end-of-dose deterioration despite "optimal" levodopa/carbidopa or levodopa/benserazide therapy; been treated with a stable regimen of 3 to 8 doses of standard release 100 mg/25 mg levodopa/carbidopa or 100 mg/25 mg levodopa/benserazide per day within at least 1 week prior to randomisation; modified Hoehn and Yahr stage of less than 5 in the OFF-state; mean duration of OFF stage ≥1.5 h during waking hours (based on historical information); concomitant anti-Parkinsonian medication (other than apomorphine, entacapone or tolcapone) in stable doses for at least 4 weeks prior to randomisation; results of clinical laboratory tests acceptable by the investigator (not clinically significant for the well-being of the subject or for the purpose of the study); able and willing to give written informed consent.

Test product, dose, administration route and batch number:
BIA 9-1067 25 mg capsules (BIAL - Portela & C[a], SA, S. Mamede Coronado, Portugal, batch numbers 080616 and 090537); oral route.
BIA 9-1067 100 mg capsules (BIAL - Portela & C[a], SA, S. Mamede Coronado, Portugal, batch numbers 080617 and 090538); oral route.

Reference product, batch number and administration route:
Placebo consisted of BIA 9-1067 matching capsules (batch number 080614); oral route.

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Concomitant therapy, dose, administration route and batch numbers:
Immediate-release 100 mg/25 mg levodopa/carbidopa tablets (Sinemet®, marketed by Merck, Sharp & Dohme, Quinta da Fonte, Paço de Arcos, Portugal, batch numbers T7112 and V6270); oral route.
Immediate-release 100 mg/25 mg levodopa/benserazide tablets (Madopar®/Restex® 125, Roche Pharma AG, Grenzach-Wyhlen, Germany, batch numbers B1283G04 and B1309G02); oral route.

Duration of treatment:
The study was to consist of four consecutive treatment periods, corresponding to the 4 different treatment options (25 mg, 50 mg and 100 mg BIA 9-1067or Placebo). In each of the four treatment periods, subjects were to be admitted to the study site 2 days prior receiving the dose of BIA 9-1067/Placebo and were to remain hospitalized ("in-patient") until 48 h after receiving the dose of BIA 9-1067/Placebo. The washout period between doses was to be at least 10 days. A follow-up visit was to occur approximately 2 weeks after the last treatment administration or early discontinuation.

Criteria for evaluation:
Pharmacokinetics:
Pharmacokinetic assessments were to be performed in the pharmacokinetics population, defined as all subjects who had valid data.
Pharmacodynamics:
Pharmacodynamics assessments were to be performed in the pharmacodynamics population, defined as all subjects who had valid data. Due to the unexpected S-COMT profiles observed for subjects #013 and #014 in both treatment periods 3 and 4, and since there was no basis for considering them as outliers, separate analyses were conducted including and excluding both treatment periods for subjects #013 (50 and 100 mg BIA 9-1067 treatment periods) and #014 (100 mg BIA 9-1067 and Placebo treatment periods).
Safety:
The safety population consisted of all subjects who received at least 1 dose of investigational product.

Statistical methods:
Summary statistics of the pharmacokinetic and pharmacodynamic parameters were reported, as appropriate, using the geometric mean, arithmetic mean, standard deviation (SD), coefficient of variation (CV), median, standard error of the mean (SEM), minimum and maximum (range). The pharmacokinetic and pharmacodynamic parameters were determined using WinNonlin® (Version 5.2) and the statistical package SAS® (Version 9.1.3) was used in computations when considered appropriate.
Pharmacokinetic parameters:
The following parameters for levodopa, 3-OMD, BIA 9-1067 and BIA 9-1079 were derived by non-compartmental analysis from the concentration versus time profiles, where appropriate: maximum observed plasma concentration (C_{max}); time of occurrence of C_{max} (t_{max}); area under the plasma concentration-time curve (AUC) from time zero to the last

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sampling time at which the drug concentration was at or above the lower limit of quantification (AUC_{0-t}) and AUC from time zero to 6 h post-dose (AUC_{0-6}), calculated by the linear trapezoidal rule; AUC from time zero to infinity ($AUC_{0-\infty}$), calculated from AUC_{0-t} + (C_{last}/λ_z), where C_{last} was the last quantifiable concentration and λ_z the apparent terminal rate constant calculated by log-linear regression of the terminal segment of the drug plasma concentration versus time curve; the apparent terminal half-life ($t_{½}$), calculated from $ln\ 2/\lambda_z$. The main levodopa and 3-OMD pharmacokinetic parameters (C_{max} and AUC_{0-6}) were compared within treatment groups and between treatment groups using an analysis of variance (ANOVA). Geometric mean ratios (GMR) and corresponding 90% confidence intervals (90% CI) for the log-transformed pharmacokinetic parameters of levodopa (C_{max} and AUC_{0-6}) obtained on Day 3 following administration of levodopa concomitantly with each different dose of BIA 9-1067 versus those obtained after administration of levodopa plus Placebo were calculated. GMR and 90% CI were also calculated for levodopa C_{max} and AUC_{0-6} obtained on Day 3 and Day 4 versus Day 2, within each treatment group. Comparison of t_{max} was done using a non-parametric technique.

Pharmacodynamic parameters based on S-COMT activity:

The following parameters concerning COMT activity (expressed as metanephrine formed by the action of the S-COMT on an epinephrine substrate) were derived from the individual COMT activity profiles: maximum inhibition of COMT activity (E_{max}), time of occurrence of E_{max} (t_{Emax}); maximum percent inhibition of COMT activity, calculated as [(E_0-E_{max})/E_0]*100, where E_0 was the baseline (pre-dose) value, and area under the effect-time curve (AUEC). The primary pharmacodynamic parameters (E_{max} and AUEC) were compared between treatments using an ANOVA with sequence, subject (sequence), treatment and period effects after logarithmic transformation of the data. GMR and 90% CI of E_{max} and AUEC following administration of levodopa concomitantly with each different dose of BIA 9-1067 versus those obtained after administration of levodopa plus Placebo were calculated. The t_{Emax} was compared using a non-parametric technique.

Pharmacodynamic parameters based on motor response:

Duration of motor response (ON duration) was defined as the interval between ON onset and the onset of wearing-OFF after the morning dose of levodopa on Days 2, 3 and 4. The ON duration, time to ON and time to best ON were analysed using survival analysis and the log-rank test. Mean ratios and 90% CI between ON time obtained on Day 3 following administration of levodopa concomitantly with each different dose of BIA 9-1067 versus that obtained after administration of levodopa plus Placebo were calculated; ON time on Day 3 and Day 4 versus Day 2 was also compared. Exploratory analyses compared the UPDRS Part III scores between treatment periods and between Day 3 and Day 4 versus Day 2.

Safety parameters:

The safety evaluation took into account the adverse events (AEs) recorded and the results of the clinical laboratory safety tests, vital signs, 12-lead ECG, modified AIMS and any other relevant parameter.

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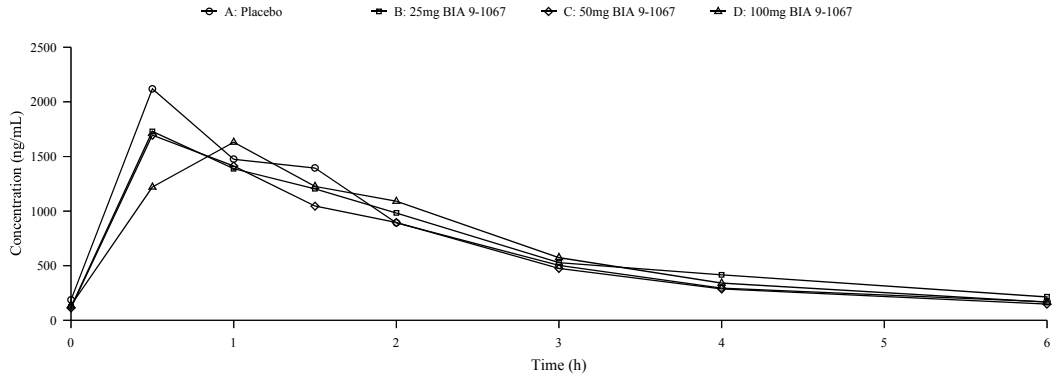
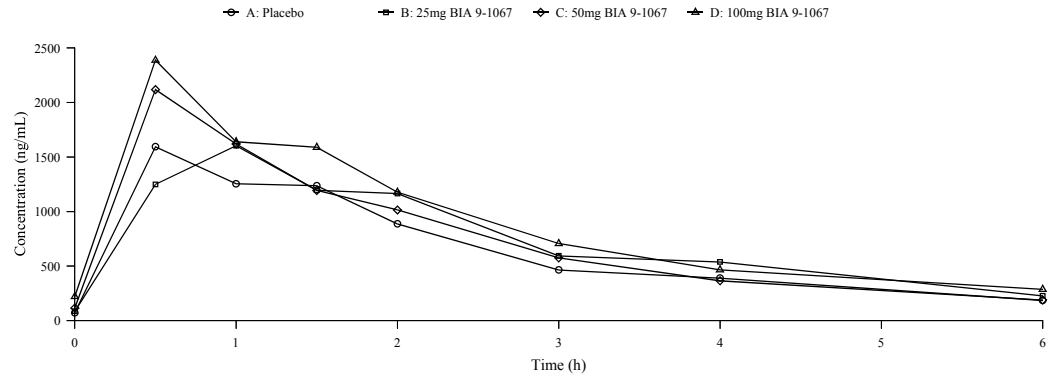
Pharmacokinetic results:

Mean plasma levodopa concentration-time profiles following an oral administration of 100/25 mg levodopa/carbidopa or 100/25 mg levodopa/benserazide administered alone on Days 2 (A) and 4 (C), and concomitantly with Placebo or 25, 50 and 100 mg BIA 9-1067 on Day 3 (B), were as follows (n=10 for all BIA 9-1067 doses, n=9 for Placebo):

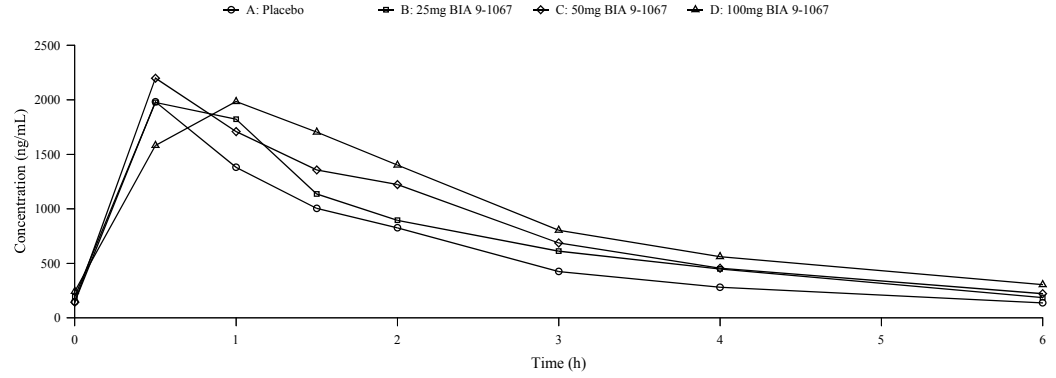
A – Day 2



B – Day 3



C – Day 4



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Mean levodopa C_{max} values were attained between 0.5 and 1 hour post-dose. BIA 9-1067 was found to increase in a dose-dependent manner the mean levodopa AUC_{0-6} values on Days 3 and 4. The PEs and 90%CI of the main pharmacokinetic parameters of levodopa following single oral administration of 100/25 mg levodopa/carbidopa or 100/25 mg levodopa/benserazide with Placebo or 25, 50 and 100 mg BIA 9-1067 on Day 3 were as follows:

	C_{max} PE (90%CI)	**AUC_{0-6}** PE (90%CI)
BIA 9-1067 25 mg / Placebo	91.43 (74.78; 111.80)	103.74 (83.30; 129.20)
BIA 9-1067 50 mg / Placebo	108.26 (88.45; 132.52)	116.41 (93.36; 145.14)
BIA 9-1067 100 mg / Placebo	129.05 (105.71; 157.53)	134.83 (108.46; 167.62)

PE = Point estimate; CI = Confidence interval

A marked increase in both rate (as assessed by C_{max}) and extent (as assessed by AUC_{0-6}) to levodopa occurred with 100 mg BIA 9-1067, as compared to Placebo. The increase in levodopa C_{max} ranged from 8.26% with 50 mg BIA 9-1067 (BIA 9-1067/Placebo ratio = 108.26 [88.45; 132.52]; means and 90%CIs) to 29.05% with 100 mg BIA 9-1067 (BIA 9-1067/Placebo ratio = 129.05 [105.71; 157.53]). There was no increase in C_{max} with the 25 mg BIA 9-1067 dose. The increase in levodopa AUC_{0-6} ranged from 3.74% with 25 mg BIA 9-1067 (BIA 9-1067/Placebo ratio = 103.74 [83.30; 129.20]) to 34.83% with 100 mg BIA 9-1067 (BIA 9-1067/Placebo ratio = 134.83 [108.46; 167.62]). No statistical differences were found for t_{max} between all BIA 9-1067 doses and Placebo. When comparing Days 3 and 4 to Day 2, a marked increase in the rate (C_{max}) to levodopa occurred with 100 mg BIA 9-1067 (Day 3 versus Day 2). A marked increase in the extent of systemic exposure (AUC) to levodopa occurred with 50 mg BIA 9-1067 (Day 4 versus Day 2). It was noticed an higher increase in AUC with 25 and 50 mg BIA 9-1067 when comparing Day 4 versus Day 2 in relation to Day 3 versus Day 2. No statistical differences were found for t_{max} when comparing both Days 3 and 4 to Day 2, for all treatments tested. A marked decrease in both rate (C_{max}) and extent (AUC) to 3-OMD occurred with 100 mg BIA 9-1067 in relation to Placebo. No statistical differences were found in both rate and extent to 3-OMD when comparing both Days 3 and 4 to Day 2. Both rate (C_{max}) and extent (AUC) of systemic exposure to BIA 9-1067 increased in a dose-dependent manner. Plasma concentrations of BIA 9-1079 were above the limit of quantification only following administration of 50 and 100 mg BIA 9-1067. Both rate (C_{max}) and extent (AUC) of systemic exposure to BIA 9-1079 increased in a dose-dependent manner following both 50 and 100 mg BIA 9-1067.

Pharmacodynamic results based on S-COMT Activity:

Mean S-COMT activity (metanephrine formed, pmol/mg protein/h) profiles from baseline (pre-dose) following an oral administration of 100/25 mg levodopa/carbidopa or 100/25 mg levodopa/benserazide concomitantly with Placebo or 25, 50 and 100 mg BIA 9-1067 on Day 3 were as follows (including #013 and #014, n=10 for all BIA 9-1067 doses, n=9 for Placebo):

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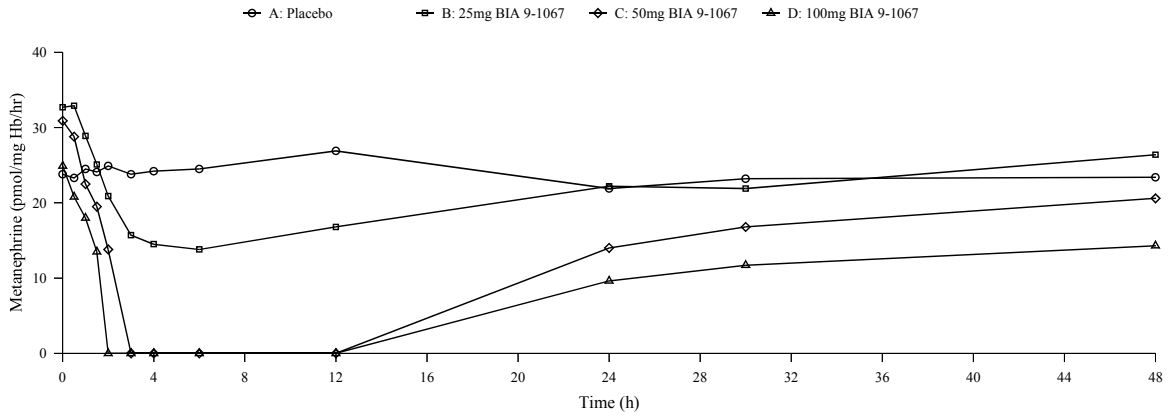

Following an oral administration of 100/25 mg levodopa/carbidopa or 100/25 mg levodopa/benserazide concomitantly with 25, 50 and 100 mg BIA 9-1067 on Day 3, maximum S-COMT inhibition (E_{max}) occurred (t_{Emax}) between 1.9 h (100 mg BIA 9-1067) and 4.65 h (25 mg BIA 9-1067) post-dose, and ranged from 67.8% (25 mg BIA 9-1067) to 100% (100 mg BIA 9-1067). All BIA 9-1067 treatments markedly inhibited in a dose-dependent manner both peak and extent of S-COMT activity in relation to Placebo.

Pharmacodynamic results based on Motor Response:

Following single oral administration of 100 mg/25 mg levodopa/carbidopa or 100 mg/25 mg levodopa/benserazide on both Days 2 and 4, and concomitantly with Placebo, 25, 50 and 100 mg BIA 9-1067 on Day 3, the pharmacodynamic results based on motor response were as follows:

- time to ON markedly decreased on Day 3 following administration of 100 mg BIA 9-1067, in relation to Placebo, and markedly increased following administration of 25 mg BIA 9-1067 when comparing both Days 3 and 4 to Day 2;
- time to best ON markedly decreased on Day 3 following administration of 50 and 100 mg BIA 9-1067, in relation to Placebo, and markedly decreased following administration of 50 mg BIA 9-1067 when comparing Day 3 to Day 2, and markedly increased following administration of 100 mg BIA 9-1067 when comparing both Days 3 and 4 to Day 2;
- total ON time duration increased 18% to 25% on Day 3 following administration of 25 and 50 mg BIA 9-1067, in relation to Placebo, respectively. However, differences between active treatments and Placebo did not attain statistical significance;
- mean total ON time without dyskinesias on Day 3 increased more than 100% following administration of 25 mg BIA 9-1067 and 73% with 50 mg BIA 9-1067, in relation to Placebo. However, differences between active treatments and Placebo did not attain statistical significance;
- mean total ON time with dyskinesias on Day 3 decreased 34% following administration of 50 mg BIA 9-1067, in relation to Placebo; an increase of 49% was observed in the mean total ON time with dyskinesias on Day 3 following administration of 100 mg BIA

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9-1067, in relation to Placebo;

- the mean UPDRS III scores were lower following administration of all BIA 9-1067 doses tested, in relation to Placebo.

Safety results:

During the course of the study, all 10 (100%) subjects who participated reported a total of 29 AEs. From these, 16 AEs were assessed as possibly related to treatment, 5 AEs as definitely related, and 8 AEs as not related. Twelve (12) AEs reported by 7 (70.0%) subjects were mild in severity, 11 AEs reported by 3 (30.0%) subjects were moderate in intensity and 6 AEs reported by 4 (40.0%) subjects were considered not applicable in intensity (abnormalities in safety laboratory parameters). From the moderate AEs, 6 AEs were reported by 2 (22.2%) subjects, 1 AE by 1 (10.0%), 3 AEs by 2 (20.0%) and 1 AE by 1 (10.0%) subjects respectively. No clinically relevant trends were seen in clinical laboratory parameters, vital signs or ECG. There were no serious adverse events or deaths. No subject discontinued due to an AE.

Conclusion:

This study in Parkinson's Disease patients was a short and single-dose study, and therefore, it was not expected that relevant changes in patient's motor response were to be found. The main objective of the study was to characterize the pharmacokinetics of levodopa in a population with Parkinson's disease. Nevertheless, it showed that BIA 9-1067, administered concomitantly with immediate release 100/25 mg levodopa/carbidopa or 100/25 mg levodopa/benserazide, increased the extent of systemic exposure to levodopa, decreased exposure to 3-OMD, decreased S-COMT activity and improved to some extent the patient's motor performance. Based on the cumulative experience with BIA 9-1067 in human pharmacology studies with healthy subjects, and taking into account the results of the current exploratory study, BIA 9-1067 appears to be a promising new COMT inhibitor and deserves further clinical evaluation in larger samples of patients.

Date of report: 15NOV2011