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:
BIA 9-1067</td></tr>
<tr><td colspan="3">Title:
A double-blind, randomised, placebo-controlled study to investigate the tolerability and the effect of three multiple-dose regimens of BIA 9-1067 on the levodopa pharmacokinetics, catechol-O-methyltransferase activity and motor response in Parkinson’s Disease patients treated with levodopa/dopa-decarboxylase inhibitor</td></tr>
<tr><td colspan="3">Clinical Study Sites and Principal Investigators:
Centre 001: Department of Neurology, Quantum Medical Center, Bucharest, Romania. Principal Investigator: Prof. Dr. Cristina Elena Mitu; Centre 002: Department of Neurology, C.M.D.T.A. NEOMED, Brasov, Romania. Principal Investigator: Prof. Dr. Magdalena Ditu; Centre 008: Clinica de Medicina Fizica si Recuperare Medicala Spitalul Clinic Judetean de Urgenta Craiova, Craiova, Romania. Principal Investigator: Prof. Dr. Cornelia Enache; Centre 005: Department of Clinical Physiology and Pathology of Extrapyramidal Nervous System SI “Institute of Gerontology, AMS Ukraine”, Kyiv, Ukraine. Principal Investigator: Prof. Dr. Iryna Karaban; Centre 007: Ukrainian State Scientific Research Institute of Medical and Social Problems of Disability, Department of Neurology and Adjustment Conditions, Dnipropetrovsk, Ukraine. Principal Investigator: Dr. Ganna Rusina; Centre 009: Department of Neuroinfections and multiple sclerosis, SI “Institute of Neurology, Psychiatry and Narcology of AMS of Ukraine”, Kharkiv, Ukraine. Principal Investigator: Prof. Dr. Nataliya Voloshyna; Centre 010: Department No. 23 of Communal setting of medical care Kharkiv’s regional clinical psychiatric hospital No. 3, Kharkiv, Ukraine. Principal Investigator: Dr. Andriy Dubenko.</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: 03FEB2010
Date of last visit: 15JUN2010</td><td>Clinical phase:
Phase II / Therapeutic Exploratory</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To investigate the effect of repeated dosing of BIA 9-1067 (5 mg, 15 mg and 30 mg, once-daily) on the levodopa pharmacokinetics, in comparison to placebo, in Parkinson’s Disease (PD) patients with motor fluctuations.
Secondary:
To investigate the tolerability and safety of repeated dosing of BIA 9-1067 (5 mg, 15 mg and 30 mg, once-daily), in comparison with placebo, in PD patients with motor fluctuations.
To investigate the effect of repeated dosing of BIA 9-1067 (5 mg, 15 mg and 30 mg, once-</td></tr>
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daily) on motor response to standard-release levodopa/carbidopa 100 mg/25 mg or levodopa/benserazide 100 mg/25 mg, in comparison with placebo, in PD patients with motor fluctuations.
To investigate the effect of repeated dosing of BIA 9-1067 (5 mg, 15 mg and 30 mg, once-daily) on erythrocyte soluble catechol-*O*-methyltransferase (S-COMT) activity, in comparison with placebo, in PD patients with motor fluctuations.
To investigate the pharmacokinetics of BIA 9-1067 following repeated dosing (5 mg, 15 mg and 30 mg, once-daily) in PD patients with motor fluctuations.

Study design and methodology:
This was a multicentre, double-blind, randomised, placebo-controlled study in four parallel groups of PD patients treated with standard-release levodopa/carbidopa 100/25 mg (Sinemet®) or levodopa/benserazide 100/25 mg (Madopar®/Restex®) and with motor fluctuations ("wearing-off" phenomenon). After a 28-day screening period, subjects were to be admitted to a 1-3 weeks baseline period to be switched respectively to standard-release levodopa/carbidopa 100/25 mg (Sinemet®) or levodopa/benserazide 100/25 mg (Madopar®/Restex®) and to adjust the number of daily doses. After the baseline period, following confirmation of eligibility, subjects were to be sequentially assigned a randomisation number that defined the treatment that was to be administered, once-daily, during the 21 to 28 days maintenance phase: Placebo, 5 mg, 15 mg or 30 mg BIA 9-1067. Subjects were to perform the first levodopa test on the morning of the day after admission, followed by the 21 to 28 days maintenance phase and a second levodopa test was to occur at the end of this maintenance phase. A follow-up visit was to occur 2 weeks after the last treatment administration or early discontinuation.

Sample size (planned and analyzed):
Planned: 32 subjects were to be enrolled. A total of 46 subjects were enrolled in the study, 40 were randomised (20 males and 20 females) and 40 received randomised study medication. Therefore, the total safety population consisted of 40 subjects, of whom 36 completed the treatment period. Two (2) subjects (5.0%) were discontinued due to adverse events (1 subject in each 15 mg and 30 mg BIA 9-1067 groups). Ten (10) subjects were exposed to each BIA 9-1067 dose (5, 15 and 30 mg) and 10 subjects were exposed to Placebo. The mean (±SD) age of the safety population was 67.5±9.04 (range: 49-88) years.

Diagnosis and main selection criteria:
At screening (admission to the baseline period): Male or female of non-childbearing potential (by reason of surgery or postmenopausal), aged ≥ 30 years; 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; modified Hoehn and Yahr stage <5 in the OFF state; mean duration of OFF state ≥1.5 h during waking hours (based on historical information); results of clinical laboratory tests acceptable by the investigator (not clinically significant for the well-being of the patient or for the purpose of the study); able and willing to give written informed consent.
At randomisation (completion of the baseline period): Been treated with a stable regimen of 3 to 8 doses per day of standard-release levodopa/carbidopa 100/25 mg (Sinemet®) or levodopa/benserazide 100/25 mg (Madopar®/Restex®) for at least 1 week prior to randomisation; mean duration of OFF state ≥1.5 h during waking hours (average of recordings of last 3 days on patient's diary); concomitant anti-Parkinsonian medication (other than apomorphine, entacapone or tolcapone) in stable doses for at least 4 weeks prior to admission.

Test product, dose, administration route and batch number:
BIA 9-1067 5 mg capsules (BIAL - Portela & C[a], SA, S. Mamede Coronado, Portugal, batch numbers 090537); oral route.
BIA 9-1067 25 mg capsules (BIAL - Portela & C[a], SA, S. Mamede Coronado, Portugal, batch numbers 090538); oral route.

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

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 V6270); oral route.
Immediate-release 100 mg/25 mg levodopa/benserazide tablets (Madopar®/Restex® 125, Roche Pharma AG, Grenzach-Wyhlen, Germany, batch numbers B1309G02); oral route.

Duration of treatment:
The study was to consist of four parallel treatment groups, corresponding to the 4 different treatment options (5 mg, 15 mg and 30 mg BIA 9-1067or placebo). In each of the four treatment groups there was to be: a 28-day screening period, a 1-3 weeks baseline period and a 21 to 28 days maintenance phase. A follow-up visit was to occur approximately 2 weeks after the last treatment administration or early discontinuation.

Criteria for evaluation:
Total population consisted of all subjects screened. Safety population consisted of all subjects who received at least one dose of investigational product including those, who did not complete the study. Pharmacodynamic (Efficacy) population consisted of all subjects who completed the second levodopa test visit. Pharmacokinetic and pharmacodynamic (S-COMT) population consisted of all subjects with valid data.
Due to the unexpected absence of BIA 9-1067 plasma concentrations and S-COMT activity/inhibition for subject #117 (15 mg BIA 9-1067 group), and as there was indeed the possibility that the subject had not swallowed the study medication, although it was given, it was decided to remove subject #117 from all PK/PD analysis. This decision was also based on the fact that the subject had a significant reduction in OFF time (possible placebo responder), which would benefit the 15 mg BIA 9-1067 group efficacy analysis.

Statistical methods:
The statistical methods for the safety and tolerability analysis as well as the part of secondary efficacy analysis (pharmacodynamic) are presented in a separate statistical analysis plan (SAP). 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 and analyses were determined using WinNonlin® (version 5.2 higher). The statistical package SAS® (Version 9.1.3) was used in computations when considered appropriate.
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 6 h post-dose (AUC_{0-6}), and AUC from time zero to the last quantified concentration (AUC_{0-t}), calculated by the linear trapezoidal rule; AUC from time zero to infinity ($AUC_{0-\infty}$), calculated from $AUC_{0-t} + (C_{last}/\lambda_z)$, where C_{last} is 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}, AUC_{0-6} and AUC_{0-t}) were compared between treatment groups using an analysis of variance (ANOVA). Geometric mean ratios (GMR) and corresponding 90% confidence intervals (90% CI) for the *log*-transformed main pharmacokinetic parameters of levodopa and 3-OMD obtained on the second levodopa test *versus* those obtained after the first levodopa test were calculated for each group. Comparison of t_{max} was done using a non-parametric technique.

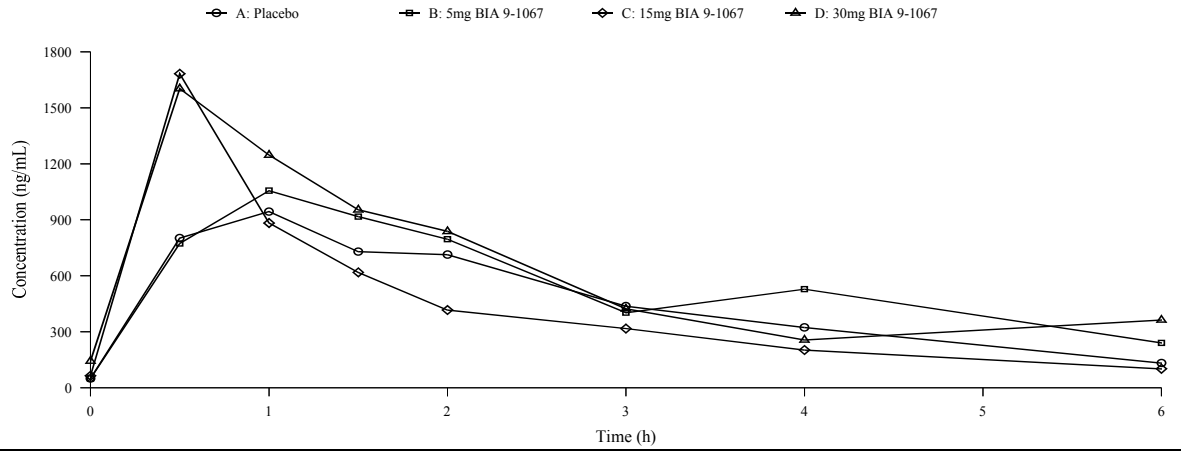
The following parameters concerning S-COMT activity (expressed as metanephrine formed by the action of the S-COMT on an epinephrine substrate) were derived from the individual S-COMT activity profiles: maximum inhibition of S-COMT activity (E_{max}), time of occurrence of E_{max} (t_{Emax}); maximum percent (%) inhibition of S-COMT activity, calculated as $[(E_0-E_{max})/E_0]*100$, where E_0 is the is the value observed before the first dose of BIA 9-1067/Placebo (Day 2), and area under the effect-time curve (AUEC). E_{max} and AUEC were compared between treatments using an ANOVA after logarithmic transformation of the data (treatment as fixed effect). GMR and 90% CI of E_{max} and AUEC obtained on the second levodopa test *versus* those obtained after the first levodopa test were calculated for each group. t_{Emax} was compared using a non-parametric technique.

For all derived variables related to motor response based on first and second levodopa tests, descriptive summary statistics are presented per levodopa test and change from first to second levodopa test. For all derived variables related to motor response based on patient diaries, descriptive summary statistics are presented per time point (Day 0-baseline, Day 7, Day 14, Day 21 and Endpoint-discharge) for the absolute values and the change from baseline during the maintenance phase. The number and proportion of responders (OFF time responders and ON time responders) are presented in frequency tables and Cochran-Mantel-Haenszel statistics was used to assess differences among treatment groups and to account for covariates.

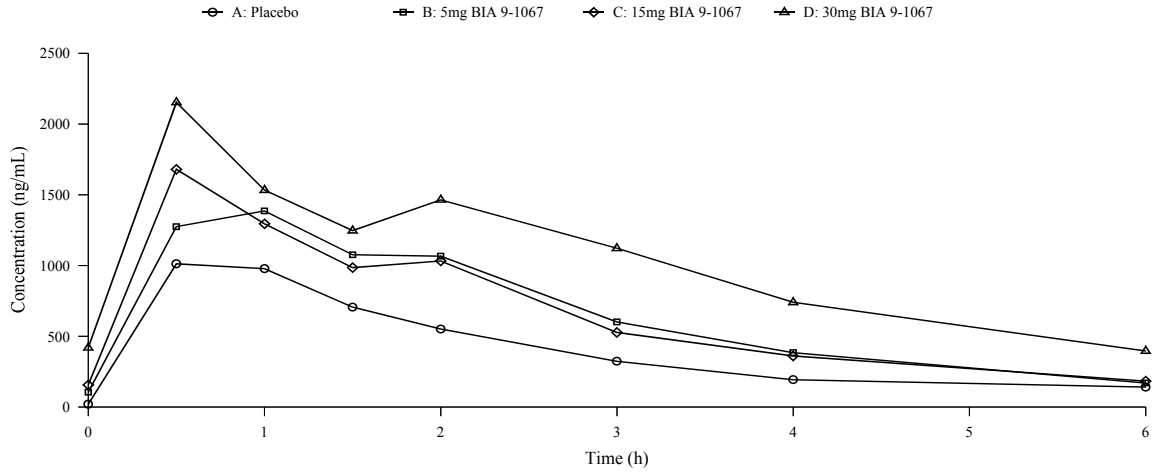
Pharmacokinetic results:

Mean plasma levodopa concentration-time profiles following oral administrations of Sinemet® 25/100 or Madopar®/Restex® 125 (**A** – first levodopa test: baseline, n=10, n=9 for 15 mg BIA 9-1067) and following a once daily oral administration of placebo, 5 mg, 15 mg and 30 mg BIA 9-1067 and Sinemet® 25/100 or Madopar®/Restex® 125 for up to 28 days (**B** – second levodopa test, n=9, n=8 for 15 mg BIA 9-1067) were as follows:

***A** – First levodopa test (baseline)*



***B** – Second levodopa test*



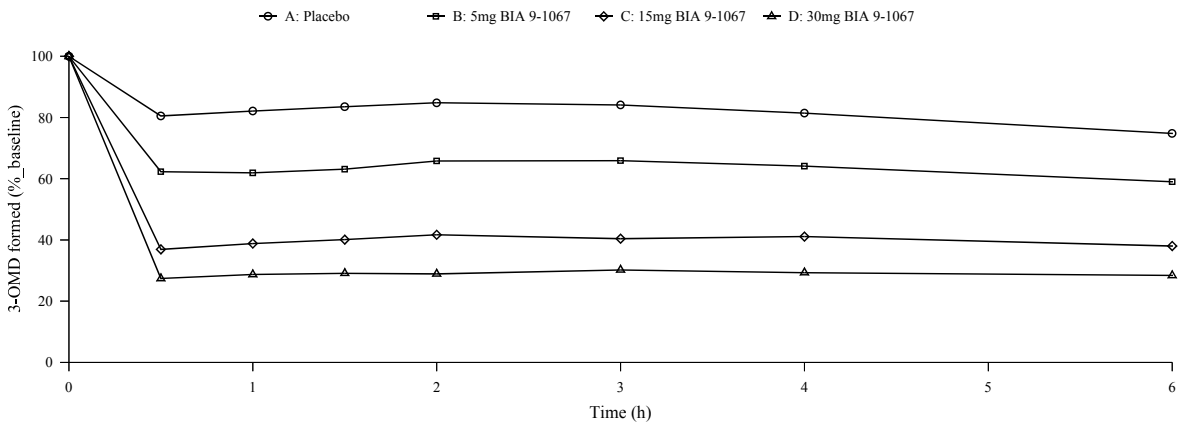
Mean levodopa C_{max} values were attained between 0.5 and 1 hour post-dose. BIA 9-1067 was found to increase in a dose-dependent manner the mean levodopa AUC_{0-6} values in relation to the baseline values: 5 mg BIA 9-1067 AUC increase = 590 ng.h/mL; 15 mg BIA 9-1067 AUC increase = 1310 ng.h/mL; 30 mg BIA 9-1067 AUC increase = 2435 ng.h/mL. The PEs and 90%CI of the mean pharmacokinetic parameters of levodopa obtained on the second levodopa test (following a once daily oral administration of placebo, 5 mg, 15 mg and 30 mg BIA 9-1067 and Sinemet® 25/100 or Madopar®/Restex® 125 for up to 28 days) *versus* those obtained at baseline (first levodopa test) were as follows:

Comparison	**C_{max}** PE (90%CI)	**AUC_{0-6}** PE (90%CI)
Placebo – SLT / baseline	80.42 (63.33; 102.11)	88.44 (69.47; 112.59)
BIA 9-1067 5 mg – SLT / baseline	133.21 (96.99; 182.95)	124.73 (95.90; 162.24)
BIA 9-1067 15 mg – SLT / baseline	108.11 (77.78; 150.26)	153.93 (104.43; 226.89)
BIA 9-1067 30 mg – SLT / baseline	148.25 (104.38; 210.56)	165.61 (125.64; 218.29)

PE = Point estimate; CI = Confidence interval; SLT = Second levodopa test

A marked increase in both rate (as assessed by C_{max}) and extent (as assessed by AUC_{0-6}) to levodopa occurred with 30 mg BIA 9-1067, as compared to baseline. The increase in levodopa C_{max} ranged from 8.11% with 15 mg BIA 9-1067 (SLT/baseline ratio = 108.11 [77.78; 150.26]; means and 90%CIs) to 48.25% with 30 mg BIA 9-1067 (SLT/baseline ratio = 148.25 [104.38; 210.56]). The increase in levodopa AUC_{0-6} ranged from 24.73% with 5 mg BIA 9-1067 (SLT/baseline ratio =124.73 [95.90; 162.24]) to 65.61% with 30 mg BIA 9-1067 (SLT/baseline ratio = 165.61 [125.64; 218.29]). No statistical difference was found for t_{max} between all BIA 9-1067 doses and Placebo.

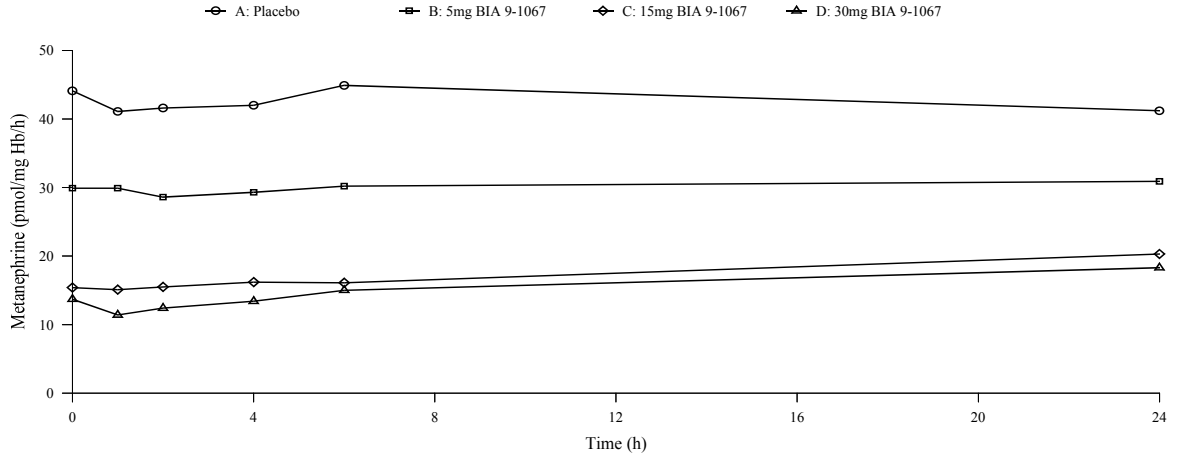
Mean plasma 3-OMD concentration-time profiles, as a percentage of change in relation to baseline, following a once daily oral administration of placebo, 5 mg, 15 mg and 30 mg BIA 9-1067 and Sinemet® 25/100 or Madopar®/Restex® 125 for up to 28 days (second levodopa test) (n=9, n=8 for 15 mg BIA 9-1067) were as follows:



A marked decrease in both rate (as assessed by C_{max}) and extent (as assessed by AUC_{0-6}) to 3-OMD occurred with all BIA 9-1067 doses, as compared to baseline. The mean decrease in 3-OMD AUC_{0-6} ranged from 37.06% with 5 mg BIA 9-1067 (SLT/baseline ratio =62.94 [50.29; 78.80]) to 71.58% with 30 mg BIA 9-1067 (SLT/baseline ratio = 28.42 [19.63; 41.16]).

Pharmacodynamic results based on S-COMT Activity:

Mean S-COMT activity (metanephrine formed, pmol/mg protein/h) profiles following a once daily oral administration of placebo, 5 mg, 15 mg and 30 mg BIA 9-1067 and Sinemet® 25/100 or Madopar®/Restex® 125 for up to 28 days (second levodopa test) were as follows (n=9, n=8 for 15 mg BIA 9-1067):



Following a once daily oral administration of placebo, 5 mg, 15 mg and 30 mg BIA 9-1067 and Sinemet® 25/100 or Madopar®/Restex® 125 for up to 28 days, maximum S-COMT inhibition (E_{max}) occurred between 0.89 h (30 mg BIA 9-1067) and 2.57 h (15 mg BIA 9-1067) post-dose (t_{Emax}), and ranged from 52.0% (5 mg BIA 9-1067) to 79.8% (30 mg BIA 9-1067). All BIA 9-1067 treatments markedly inhibited both peak and extent of S-COMT activity in relation to placebo. Peak and extent of S-COMT inhibition were dose-dependent.

Pharmacodynamic results based on efficacy:
Following a once daily oral administration of placebo, 5 mg, 15 mg and 30 mg BIA 9-1067 and Sinemet® 25/100 or Madopar®/Restex® 125 for up to 28 days, the pharmacodynamic results based on efficacy were as follows:

Motor response based on changes between first and second levodopa tests

- the mean (SD) ON duration increased of 28.4 (50.84) min with 5 mg BIA 9-1067, 43.8 (40.71) min with 15 mg BIA 9-1067, 73.4 (121.93) min with 30 mg BIA 9-1067 and 22.2 (47.35) min with placebo.
- there was a decrease in mean (SD) onset latency (time to ON) of 12.2 (30.18) min with 5 mg BIA 9-1067, 6.3 (20.83) min with 15 mg BIA 9-1067 and 3.2 (8.07) min with 30 mg BIA 9-1067. There was no change for the onset latency with placebo.
- it was also observed a mean (SD) peak latency (time to best-ON) decrease of 15.1 (37.78) min with 5 mg BIA 9-1067, 12.1 (38.47) min with 15 mg BIA 9-1067, 3.8 (12.76) min with 30 mg BIA 9-1067 and 7.9 (19.11) min with placebo.

Motor response in maintenance phase (patient diaries)

- the mean (SD) total daily OFF decreased 3.3 (108.02) min, 15.6 (85.57) min, 116.9 (115.04) min and 145.0 (167.26) min, corresponding to a percentage decrease of 0.77%, 4.16%, 29.55% and 32.71% with placebo, 5 mg, 15 mg and 30 mg BIA 9-1067, respectively.
- the mean (SD) percentage of ON time without troublesome dyskinesia increased, in relation to baseline, 2.2% (9.46), 12.3% (11.20), and 15.6% (15.42) with 5 mg, 15 mg and 30 mg BIA 9-1067, respectively. There was a decrease of 1.1% (12.31) with placebo
- OFF time responder rate was 11.1%, 33.3%, 87.5% and 66.7%, with placebo, 5 mg (p=0.3261), 15 mg (p=0.0024) and 30 mg (p=0.0090) BIA 9-1067 respectively.
- ON time responder rate was 33.3%, 33.3%, 87.5% and 77.8%, with placebo, 5 mg (p=0.7518), 15 mg (p=0.0203) and 30 mg (p=0.0323) BIA 9-1067 respectively.
- the daily number of doses of levodopa/DDCI was the same in each group and during the entire treatment period of the study.

Investigator's and Patient's Global Assessment of Change

- the percentage of subjects whose change was assessed as "Very much improved" or "Much improved" by the Investigator was 22.2%, 44.4%, 62.5% and 66.7% with placebo, 5 mg, 15 mg and 30 mg BIA 9-1067, respectively;
- the percentage of subjects who self-assessed change as "Very much improved" or "Much improved" was 44.4%, 33.3%, 75.0% and 77.8% with placebo, 5 mg, 15 mg and 30 mg BIA 9-1067, respectively.

Unified Parkinson's Disease Rating Scale (UPDRS) – Sections I, II, III, V and VI

- no major differences were observed in the mean UPDRS scores when comparing BIA 9-1067 with placebo. Nevertheless, the mean UPDRS I, II and III scores were consistently numerically lower following administration of 5 mg, 15 mg and 30 mg BIA 9-1067, in relation to placebo.

Safety results:
All treatments tested in this study were generally well tolerated. During the course of the study, 11 (27.5%) subjects who participated reported a total of 28 adverse events. From these adverse events, 14 AEs were assessed as possibly related to treatments. Thirteen (13) AEs reported by 8 subjects were mild in severity, 12 AEs reported by 6 subjects were moderate in intensity, 1 AE (toothache) was severe in intensity and 2 AEs reported by 1 subject were considered not applicable in intensity. Following the treatment groups of placebo, 5 mg, 15 mg and 30 mg BIA 9-1067, the most frequent adverse events were dizziness (2 cases, 1, 1 and 0, respectively) and nausea (0 cases, 0, 1 and 3, respectively). The UPDRS Section IV showed that BIA 9-1067 did not increase the complications of therapy. There were no serious adverse events or deaths. Two (2) subjects (5.0%) were discontinued due to adverse events (1 subject in each 15 mg and 30 mg BIA 9-1067 groups). Subject #101 (15 mg BIA 9-1067 group), due to the occurrence of dizziness (moderate), depression (mild), nausea (mild), bradyphrenia (moderate), fatigue (mild) and increase of OFF duration (moderate) was withdrawn from study participation and all AEs were considered as possible related to study medication. Subject #121 (30 mg BIA 9-1067 group), due to the aggravation of dyskinesias (moderate) was withdrawn from study participation and the AE was considered as possible related to study medication.

Conclusion:
This phase IIa study in Parkinson's disease patients with "wearing-OFF" phenomenon showed that all BIA 9-1067 doses (5, 15 and 30 mg), administered once-daily for up 28 days with standard release levodopa/DDCI 100/25 mg, increased the extent of systemic exposure to levodopa, decreased exposure to 3-OMD and decreased S-COMT activity. The study was not designed to detect any significant differences in motor performance, but the exploratory analysis performed shows improvement in various motor outcomes, including a dose dependent change in absolute OFF time. Results were highly consistent across the multiple analyses performed and showed that 30 mg BIA 9-1067 tended to be the most efficacious treatment tested, followed by 15 mg BIA 9-1067. All treatments were generally well tolerated and safe. 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: 31DEC2010