2.0 SYNOPSIS

Name of Sponsor/Company: BIAL - Portela & C[a], S.A.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Not assigned	**Volume:**	
Name of Active Ingredient: Opicapone	**Page:**	
Title of Study: Efficacy and safety of BIA 9-1067 in idiopathic Parkinson's disease patients with "wearing-off" phenomenon treated with levodopa plus a dopa decarboxylase inhibitor (DDCI): a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical study (Part II - Open-Label Extension Phase).		
Protocol number (study name): BIA-91067-302 (BIPARK II)		
Coordinating Investigator: Professor Andrew Lees, MD, FRCP, FMedsCI, National Hospital for Neurology and Neurosurgery, Queens Square, London, WC1N 3BG, UK.		
Study center(s): 64 investigational sites in 11 countries (Argentina, Australia, Belgium, Chile, Estonia, India, Israel, Korea, Russia, South Africa, and United Kingdom) participated in the open-label (OL) extension phase of the study.		
Publication (reference): None.		
Studied period (years): 18 March 2011 (first subject, first visit, double-blind [DB] period), 01 July 2011 (first subject, first visit, OL period) to 25 June 2013 (last subject, last visit, OL period).	**Phase of development:** III	
Objectives: The objective of Part II, the Open Label Extension Phase of the study, was to investigate the safety, tolerability and maintenance of therapeutic effect of opicapone (OPC) (25 mg QD or 50 mg QD) adjusted according to clinical response over 1 year of treatment, when administered with the existing treatment of levodopa (L-DOPA) plus a DDCI, in Parkinson's disease (PD) patients with end-of-dose motor fluctuations who completed the Part I Double Blind Phase of the study.		

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Methodology:

The study was designed to include two periods, a double-blind (DB) period and an open-label (OL) period: only the OL period is described in this report. The results of the DB period are presented in a separate report.

After a screening period of up to two weeks, eligible subjects entered the DB treatment period and were randomly assigned to one of the three treatments (Placebo, OPC 25 mg, or OPC 50 mg) at Visit 2 (V2) using a 1:1:1 ratio. Study medication was administered in combination with existing treatment of L-DOPA/ DDCI. From V2 to V4 of the DB period (first 2-3 weeks of the DB period), the Investigator could decrease the daily dose of L-DOPA dose (keeping the number of daily intakes unchanged), according to subject response. If needed, the L-DOPA dose could be increased again up to the baseline level. The dosage of L-DOPA was not to be changed during the study from V4 through to the end of the DB period. After completion, subjects who did not enter the OL period were to have a post-study visit within 14 days.

The OL period started on the day after V7 and ended at V14 (52 weeks). All subjects were to begin OL treatment at a dose of 25 mg/day OPC for the first week (until V8). If "wearing off" was not sufficiently controlled and tolerability allowed, the OPC dose could be adjusted by titrating up to 50 mg/day. If unacceptable dopaminergic adverse events (AEs) were seen, the L-DOPA dose was to be adjusted. If not sufficient to manage the AEs, the OPC dose could then be down titrated. For other AEs, the same titration procedure could be applied or OPC dose adjustments implemented. From V13 to V14 (6 weeks to the end of the OL period), L-DOPA and OPC doses were to remain stable.

Number of subjects (planned and analyzed):

It was planned to randomize 405 subjects to achieve 135 subjects in each of the three treatment groups.
Consented: 485 subjects.
Randomized into the DB period: 427 subjects.
Enrolled into the OL period: 367 subjects.
OL Safety Set (SS): 353 subjects.
OL Full Analysis Set (OL-FAS): 339 subjects.

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Diagnosis and main criteria for inclusion:

Male and female subjects between 30 and 83 years old, inclusive, who had a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for at least three years, with the presence of recognizable ON and OFF states (motor fluctuations) and an average total daily OFF-time while awake of at least 1.5 hours. The disease severity at ON had to be rated as Stage I-III using the modified Hoehn &Yahr staging of PD and subjects were to have been treated with L-DOPA/DDCI (three to eight daily doses, which could include a slow-release formulation) for at least one year with clear clinical improvement.

Subjects with a dyskinesia disability score of >3 in the Unified Parkinson's Disease Rating Scale (UPDRS) sub-section IV A item 33 were not permitted to enter the study, neither were subjects with severe and/or unpredictable OFF periods.

Subjects who remained on study treatment at V7 could enter the OL period.

Test product, dose and mode of administration, batch number:

25 mg OPC capsules for oral administration once daily.
50 mg OPC capsules for oral administration once daily.
For batch numbers, see Appendix 16.1.6.

The investigational medicinal product (IMP) was to be taken in the evening and administered at least one hour after the last daily dose of L-DOPA/DDCI. Subjects had to fast for one hour before and for at least one hour after intake of IMP.

Duration of treatment:

Total duration of the OL treatment for an individual subject was 1 year. Part I of the study consisted of a DB treatment of 14- to 15- weeks. The total duration of treatment for an individual subject in this study was therefore up to 67 weeks.

Reference therapy, dose and mode of administration, batch number:

Not applicable to the OL period.

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Criteria for evaluation:

Efficacy:

Subject diary charts for ON/OFF periods; UPDRS; Investigator's and subject's assessments of change; Parkinson's Disease Sleep Scale (PDSS); Parkinson's Disease Questionnaire-39 (PDQ-39); Non-motor Symptoms Scale (NMSS).

Safety:

Adverse events (AEs), laboratory safety tests, physical and neurological examinations, skin examination for melanoma, vital signs, electrocardiogram (ECG), Columbia Suicide Severity Rating Scale (C-SSRS) and modified Minnesota Impulsive Disorders Interview (mMIDI).

Statistical methods:

Efficacy analyses:

Efficacy data for the OL period were generally summarized using descriptive statistics for the different parameters at the different visits of the OL period and respective changes to DB and OL baselines.

Maintenance of treatment effect from the end of the DB period through to the end of the OL period was assessed by exploratory analysis of absolute OFF-time in subjects in the OL-FAS who were randomized to OPC in the DB period (excluding subjects who received placebo during the DB period). The difference in OFF-time between OL baseline and at V14 was estimated using a linear model with pooled country as a factor.

Exploratory analysis to assess dose effect on the absolute OFF-time was conducted. At each scheduled OL visit, each subject was assigned a dose (25 mg or 50 mg, depending on the dose dispensed at the visit immediately prior to the scheduled assessments). A linear model with mixed effects was fitted to the data with pooled country as a fixed effect, subject as a random effect and dose of OPC and OL baseline OFF-time as covariates.

Summary statistics were also presented by visit and treatment (OPC or Placebo) in the DB period, for change from OL baseline in absolute OFF-time and, ON-time with troublesome, non-troublesome and without dyskinesia.

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Safety analyses:
All safety parameters were presented using descriptive statistics. The analyses focused on treatment-emergent AEs (TEAEs) and were categorized by System Organ Class (SOC) and Preferred Term (PT). Serious TEAEs, TEAEs leading to death and TEAEs resulting in discontinuation of study treatment were tabulated using frequency tables. For laboratory parameters, descriptive analyses at each time point and change from OL baseline to each post-baseline time point were presented. Values of vital signs and 12-lead ECGs, including change from baseline were summarized. Frequency tables and subject listings were presented for markedly abnormal values. Shift tables were presented according to reference ranges (low, normal or high).

Summary:

Efficacy Results:

The therapeutic effect of OPC was maintained and even slightly improved over the 1-year study duration. At the end of the OL period, the OFF-time reduction relative to the DB baseline was above 2 hours (-126.2 mins), which was accompanied by an increase of ON-time without troublesome dyskinesia (109.6 mins). The proportion of OFF- and ON-time responders (relative to DB baseline) was 68.4% and 65.8%, respectively, slightly above the rate observed at the end of the DB period. Subjects who received placebo or OPC during the DB period both experienced further reductions of OFF-time after the start of OL OPC and, as expected, greater changes were observed for subjects who initially received DB Placebo (-35.5 mins), compared to subjects who received DB OPC (-14.6 mins). Of note, compared to DB baseline, greater sustained OFF-time reductions were observed for subjects who received DB OPC. At V14, the OFF-time reduction for subjects who received DB OPC was -139.8 mins compared to -101.0 mins for subjects who received DB Placebo. This may suggest efficacy benefits of early initiation of OPC compared to delayed initiation. For disease and symptom scales (UPDRS, PDQ-39 and NMSS), overall the mean scores improved initially up to 6 months of treatment, and at the end of the OL period were still slightly improved, despite disease progression. The PDSS score had only minimally worsened compared to DB baseline. The mean daily L-DOPA dose was maintained below the baseline value, despite the fact that investigators could adjust subjects' treatment according to the clinical response. At the end of the OL period, the mean L-DOPA dose was decreased -35.6 mg compared to the DB baseline.

In addition, the benefits of OPC treatment were still well perceived by subjects and investigators after 1 year of treatment, as reflected by the global evaluation scores, with positive ratings in about two-thirds of the subjects at the end of the study.

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Name of Active Ingredient: Opicapone (2,5-dichloro-3-[5-{3,4-dihydroxy-5-nitrophenyl}-1,2,4-oxadiazol-3-yl]-4,6-dimethylpyridine 1-oxide)	**Page:**	

Safety Results:

Dopaminergic AEs or other Parkinson's disease symptoms were the most commonly reported TEAEs during the study. Dyskinesia was the most frequent AE (21.5% of the subjects), followed by (worsening) PD (17.0%), fall (9.1%), blood CPK increased (7.4%), insomnia (5.7%) and orthostatic hypotension (5.4%). The majority of TEAEs were mild to moderate in severity and the types and incidence of TEAEs over the course of the study did not reveal safety concerns related to the long-term use of OPC. Worsening parkinsonism was more commonly reported in the OL period compared to the DB period, but this is most likely due to disease progression rather than treatment.

Five deaths were reported during the OL period: septic shock (unrelated), small cell lung cancer (unrelated), cerebral hemorrhage after traumatic brain injury (possible related), cerebral hemorrhage (unrelated) and unknown cause (unrelated). A total of 40 (11.3%) subjects reported at least one SAE. At the PT level, no SAEs were reported by more than two subjects. Few subjects (9.1%) prematurely withdrew from the OL period due to an AE. Dopaminergic events (dyskinesia 0.8%; hallucinations 0.8%; orthostatic hypotension 0.3%) and aggravation of PD (0.6%) accounted for most of discontinuations potentially related to OPC treatment. Skin cancers were reported in 9 (2.5%) subjects, with two cases of melanoma (Note: one case was subsequently determined after database lock not to be melanoma following biopsy results). There were no reports of myocardial infarction, prostate cancer or any serious hepatic event. There were no reports of severe diarrhea.

For the majority of laboratory parameters there were no substantial changes across visits. As observed in the DB period, a trend was maintained towards slightly decreased hemoglobin levels and increased blood CPK. However, the incidence of clinically significant findings was low and most abnormalities were of mild intensity.

There were no relevant findings for liver function tests: there was one single report of ALT ≥3 x upper range limit (URL) (3.4 x URL), and other of a total bilirubin ≥2 x URL (2.3 x URL). Importantly, there were no potential Hy's law cases.

Few significant findings were observed for neurological and physical examinations, vital signs (blood pressure, heart rate and body weight), as well as for ECG parameters.

No subject committed suicide, attempted suicide or had other suicidal behavior and the C-SSRS showed no effect on suicidality. Impulsive disorders as screened with the mMIDI were reported in few subjects.

Conclusions:

Long-term use of OPC over 1-year of treatment in the dose range 25 mg to 50 mg was safe, well tolerated, and presented sustained efficacy in reducing the OFF-time in PD patients with motor fluctuations on L-DOPA therapy.