2 SYNOPSIS

Sponsor: BIAL - Portela & C[a], S.A.

Product: Opicapone (BIA 9-1067)

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

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- and active-controlled, parallel-group, multicentre clinical study.

Investigator: The coordinating Investigator of this multicentre study was Prof. Dr. Joaquim Ferreira.

Clinical phase: III

Reporting period: Double-blind (DB) period only

Study duration and dates:

The duration per subject was up to 71 weeks: up to 2 weeks of Screening, 14 to 15 weeks of the DB period, 52 weeks of the open-label (OL) period, and 2 weeks of the safety Follow-up.

The recruitment period was approximately 28 months, first subject in was 31 Mar 2011 and last subject out (from DB period) was 30 Nov 2013.

Objectives:

The *primary objective* of the study was to assess the efficacy of 3 different doses of opicapone (BIA 9-1067) (5 mg, 25 mg, and 50 mg) administered once daily, compared with placebo or 200 mg of entacapone, when administered with the existing treatment of levodopa (L-DOPA) plus a DDCI, in patients with Parkinson's disease (PD) and end-of-dose motor fluctuations.

The *secondary objectives* of the study were to investigate the safety and tolerability of the combined treatment (L-DOPA/DDCI plus opicapone, entacapone, or placebo).

Methodology:

This was a Phase III, multicentre, DB, randomised, placebo- and active-controlled, parallel-group study conducted in adults diagnosed with idiopathic PD. The study consisted of the following periods:

- A Screening period of up to 2 weeks.
- A DB period of 14 to 15 weeks.
- An OL extension period of 1 year.

- A Follow-up period of approximately 2 weeks.

The Screening and DB periods comprised Part I of the study; the OL period comprised Part II. In the following, only the procedures and results related to Part I of the study are described. Details and results of Part II are not included in this report and will be reported separately.

The DB period of the study had 5 treatment arms: 3 opicapone groups, each receiving 1 of 3 different doses (5 mg, 25 mg, or 50 mg QD); the active comparator group receiving 200 mg of entacapone with each L-DOPA/DDCI intake; and a placebo group. At Visit (V) 2, eligible subjects were randomly assigned to treatments using a 1:1:1:1:1 ratio. The investigational medicinal product (IMP) was administered with existing treatment of L-DOPA/DDCI.

From V2 to V4 of the DB period, the Investigator could decrease the daily dose of L-DOPA/DDCI (keeping the number of daily intakes unchanged), according to subject response. The dose could be increased again, but was not to exceed the baseline dose level. The dosage of L-DOPA/DDCI was not to be changed from V4 through the end of the DB period.

Number of subjects (total and for each treatment):

The study planned to randomise approximately 550 subjects (110 subjects in each treatment group) and a total of 600 subjects were actually randomised: 121 subjects to placebo, 122 to entacapone, 122 to opicapone 5 mg, 119 to opicapone 25 mg, and 116 to opicapone 50 mg.

Diagnosis and main criteria for inclusion:

Subjects were included in the study if they met all of the following inclusion criteria:

<u>V1 (Screening, up to 14 days before V2)</u>

- Able to comprehend and willing to sign an informed consent form.
- Male and female subjects between 30 and 83 years old, inclusive. Note, for subjects in the Czech Republic, the age range was between 30 and 64 years old, inclusive, between implementation of Local Amendment #2 (23-Feb-2011) for the Czech Republic and Amended Protocol for Czech Republic, Final Version 4.0, which reinstated the original age range).
- Diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for at least 3 years.
- Disease severity Stages 1 to 3 (modified Hoehn and Yahr staging) at ON.
- Treated with L-DOPA/DDCI for at least 1 year with clear clinical improvement as per Investigator's judgment.
- Treated with 3 to 8 daily doses of L-DOPA/DDCI, which could have included a slow-release formulation.
- On a stable regimen of L-DOPA/DDCI and other anti-PD drugs for at least 4 weeks before Screening.

- Signs of "wearing-off" phenomenon (end-of-dose deterioration) for a minimum of 4 weeks before Screening, with average total daily OFF-time while awake of at least 1.5 hours, excluding the early morning pre-first dose OFF, despite optimal anti-PD therapy (based on the Investigator's judgment).
- Able to keep reliable diaries of motor fluctuations (alone or with family/caregiver assistance).
- Amenorrheic for at least 1 year or surgically sterile for at least 6 months before Screening. Females of childbearing potential were required to be using an effective non-hormonal contraceptive method.

V2 (Randomisation, Day 0)

- Have filled-in self-rating diary charts in accordance with the diary chart instructions and with ≤3 errors per day.
- At least 1.5 OFF hours per day, excluding the early morning pre-first dose OFF period (i.e. the time between wake-up and response to the first L-DOPA/DDCI dosage), as recorded in the self-rating diary for at least 2 of the 3 days preceding V2.
- Results of the Screening laboratory tests were considered acceptable by the Investigator (i.e. not clinically relevant for the well-being of the subject or for the purpose of the study).

Patients with non-idiopathic PD, a dyskinesia disability score >3, severe and/or unpredictable OFF periods, previous use of entacapone, or a history of neuroleptic malignant syndrome (NMS), NMS-like syndromes, or non-traumatic rhabdomyolysis were to be excluded from the study.

Test and reference products, dose and mode of administration, batch number:

The IMPs to be tested in this study were opicapone as the research therapy and entacapone and placebo as the reference therapies. Opicapone was supplied in capsules of 5 mg (batch numbers: 100335, 110052, 110440, 120125), 25 mg (batch numbers: 100337, 100928, 110053, 110441, 110830, 120126, 120364, 120455, 120456, 120707, 120708) and 50 mg (batch numbers: 100338, 100339, 110054, 110442, 110452, 110831, 120025, 120026, 120027, 120028, 120451, 120709, 120710, 120711). Entacapone was supplied in 200 mg tablets (batch numbers: U0034, U0035, U0037, U0038, U0039, U0041). Placebo capsules were identical capsules with filler (batch numbers: 5348.12, 2101.11.0861).

To ensure blinding during the DB period, the opicapone capsules and entacapone tablets were identically over-encapsulated and taken orally. The placebo capsules were prepared by filling identical capsules with filler (also used as back-filling).

During the DB period, subjects were to take 1 capsule of IMP concomitantly with each L-DOPA/DDCI dose (3 to 8 daily doses). An additional IMP bedtime dose was to be administered at least 1 hour after the last daily dose of L-DOPA/DDCI.

Duration of treatment:

Total duration of the DB treatment for an individual subject was 14- to 15-weeks. At the end of the DB period, subjects could enter a 1-year open-label extension in which all subjects

were to be treated with OPC. The total duration of treatment for an individual subject in this study was therefore up to 67 weeks.

Criteria for evaluation:

Efficacy: The primary efficacy variable was the change in absolute OFF-time from baseline to the end of the DB period (endpoint), measured as the average absolute OFF-time reported in subject's Hauser diaries in the 3-day period preceding each visit.

The key secondary efficacy variables were:

- OFF-time responders: 1 hour or more reduction in absolute OFF-time from baseline to endpoint.
- ON-time responders: 1 hour or more increase in absolute ON-time from baseline to endpoint.

Other secondary efficacy variables were:

- Absolute OFF-time at the different visits of the DB period and change from baseline until endpoint.
- Percentage OFF-time at the different visits of the DB period and change from baseline until endpoint (calculated as the sum in minutes from 30-minute periods classified as OFF divided by the total time awake).
- Absolute and Percentage ON-time at the different visits of the DB period and change from baseline until endpoint, for the following ON-time categories:

  - Total ON

  - ON-time without dyskinesia.

  - ON-time with non-troublesome dyskinesia.

  - ON-time with troublesome dyskinesia.

  - ON-time without troublesome dyskinesia (ON-time with non-troublesome dyskinesia + ON-time without dyskinesia).
- Frequency of OFF-time responders at the different visits of the DB period until endpoint.

Additional secondary efficacy outcomes include the Unified Parkinson's Disease Rating Scale (UPDRS), the Parkinson's Disease Sleep Scale (PDSS), the Parkinson's Disease Questionnaire (PDQ-39), the Non-motor Symptoms Scale (NMSS), and the Investigator's and Subject's Global Assessment of Change.

Safety: Safety was evaluated based on the adverse events (AEs), standard laboratory safety data (haematology, biochemistry, urinalysis), 12-lead electrocardiogram (ECG), vital signs (blood pressure, heart rate), physical and neurological examinations, the Columbia Suicide Severity Rating Scale (C-SSRS), and the Modified Minnesota Impulsive Disorders Interview (mMIDI).

Statistical methods:

Efficacy analysis:

Primary efficacy analysis:

The primary efficacy analysis focused on identification of at least 1 efficacious dose of opicapone and its subsequent comparison with the active control, entacapone, with regard to the mean reduction in absolute OFF-time from baseline to the end of the DB period.

One-sided tests were used to test superiority vs. placebo in the Full Analysis set (FAS) and non-inferiority vs. entacapone in the Per-protocol (PP) set, where the non-inferiority margin was defined as 30 minutes. In order to control for multiplicity, a sequential gatekeeping procedure was used. The family-wise error rate (joint level of significance of all tests) was 0.025 (corresponding to 0.05 for 2-sided tests). For each dose of opicapone, the non-inferiority vs. entacapone was tested only if the efficacy of opicapone vs. placebo had been established.

For both the superiority and non-inferiority tests, an analysis of covariance (ANCOVA) model with a common error variance was used to generate adjusted estimates and test statistics. The model included treatment group and region as fixed effects and baseline OFF-time as a covariate.

Secondary efficacy analyses:

Secondary efficacy analyses were used to support the primary efficacy analysis and to present additional efficacy data in an exploratory way. Two-sided p-values and corresponding 95% confidence intervals (CIs) were used as descriptive measures of treatment group differences.

For the analysis of the key secondary efficacy variables, pairwise Cochran-Mantel-Haenszel tests stratified by region were carried out to compare the responder rates in each of the opicapone dose groups vs. placebo and in the entacapone group vs. placebo.

For the analysis of other secondary efficacy variables, summary statistics are presented. Changes in variables from baseline to endpoint were analysed using ANCOVA with different combinations of fixed effect factors and covariates.

Safety analysis:

All safety analyses were analysed descriptively and presented by actual treatment group and pooling the opicapone groups. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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 IMP were tabulated using frequency tables.

For laboratory parameters, descriptive analyses at each time point and of changes from baseline to each post-baseline time point were presented by treatment group. Values of vital signs and 12-lead ECGs, including changes from baseline were also summarized. Frequency and shift tables were presented for clinically significant abnormalities according to the Investigator, and markedly abnormal values according to sponsor's prespecified criteria.

Results:

A total of 600 subjects were randomized in the DB period: 121 to placebo, 122 to entacapone, 122 to opicapone 5 mg, 119 to opicapone 25 mg, and 116 to opicapone 50 mg. The completion rate was high and comparable across all treatment groups: 90.9% for placebo, 87.7% for entacapone, and between 90.2% and 92.2% for the 3 opicapone doses. The most common reason for discontinuation was AEs: 6.6% for placebo, 6.6% for entacapone, 5.7% for opicapone 5 mg, 6.7% for opicapone 25 mg, and 4.3% for opicapone 50 mg.

Demographics and baseline characteristics:

The demographic characteristics at baseline were similar across the treatment groups in the Safety set, the FAS, and the PP set. In the Safety set, roughly 60% of subjects in all treatment groups were male, the mean age was between 63.5 and 64.4 years, roughly 70% were younger than 70 years, and all subjects were Caucasian. The mean body mass index ranged from 26.4 kg/m^2 to 27.1 kg/m^2.

Baseline PD characteristics did not differ significantly between the treatment groups for most characteristics in the FAS. The mean duration of PD ranged between 6.99 and 7.71 years across the treatment groups, and the onset of motor fluctuations began a mean of 2.16 to 2.32 years before subjects were included in the study. Baseline absolute OFF-time ranged between 6.2 and 6.9 hours. Dyskinesia was present at baseline in between 41.7% and 47.1% of subjects across the treatment groups. Part III UPDRS scores at ON state ranged between 25.8 and 29.0 points, while total UPDRS ranged between 35.4 and 40.1 points. The mean Hoehn and Yahr scores ranged between 2.3 and 2.4 and the mean Schwab and England scores ranged between 81.9% and 82.9%.

A similar proportion of subjects used either L-DOPA/carbidopa or L-DOPA/benserazide at study entry. The mean L-DOPA daily dose at baseline ranged from 642 mg/day to 695 mg/day across the treatment groups. The vast majority of subjects (more than 90% of the subjects in all treatment groups) used predominantly immediate release formulations rather than controlled release formulations.

A somewhat lower proportion of subjects in the opicapone 5 mg group (69.7%) were taking anti-PD medications (other than L-DOPA) compared to the other treatment groups (between 80.0% and 82.5%). More than 2/3 of the subjects in the other 4 groups were taking dopamine agonists (67.2% to 73.3%) compared to 58.0% of opicapone 5 mg subjects, roughly 1/4 were taking amantadine (22.6% to 25.0%) compared to 17.6%, roughly 20% were taking monoamine oxidase inhibitors (19.2% to 23.3%) compared to 16.8%, and 5% to 7% were taking anticholinergics compared to 2.5%. This proportion of subjects and type of anti-PD medications remained essentially unchanged throughout the study.

Efficacy results:

The results of the primary and secondary efficacy variables analysed in the FAS and PP set present a consistent picture of the effect of opicapone, compared to both placebo and the active comparator entacapone. Analysis of the primary efficacy variable showed that the mean change from baseline in absolute OFF-time at endpoint was largest in the opicapone 50 mg group (-116.8 minutes), followed by the entacapone (-96.3 minutes), opicapone 5 mg (-91.3 minutes) and opicapone 25 mg (-85.9 minutes) groups, and was smallest in the

placebo group (-56.0 minutes) in the FAS, with similar results in the PP set. The stepwise gatekeeping procedure used to assess the superiority of opicapone vs. placebo and non-inferiority vs. entacapone for the change in absolute OFF-time showed that opicapone 50 mg was both superior to placebo in the FAS (local p-value 0.0005, adjusted p-value 0.0015) and non-inferior to entacapone in the PP set (local p-value 0.0017, adjusted p-value 0.0052, based on a the non-inferiority margin of 30 minutes). The estimates of the difference (-26.2 minutes with an upper bound for the unadjusted 95% CI of 11.4 minutes) indicate a tendency for greater OFF-time reductions compared to entacapone. As expected, entacapone was superior to placebo, with a treatment difference of -40.3 minutes (p=0.0141, unadjusted 1-sided t-test at a 2.5% level of significance).

The exploratory, supportive, and sensitivity analyses were all consistent and confirmed the robustness of the primary analysis. The results of the different subgroup analyses showed that opicapone is effective in decreasing OFF-time regardless of age, gender, region, disease duration or severity, or use of other anti-PD drugs, with no interaction with treatment for any of these factors.

The results from the diary-reported secondary efficacy endpoints also supported those of the primary analysis. The OFF-time reduction was accompanied by an increase in ON-time, most of which was without dyskinesia. Only a very small percentage of overall awake time was ON-time with troublesome dyskinesia (≤3% at any visit).

The Investigator's and Subject's Global Assessments of Change both showed a higher proportion of opicapone subjects with improvements at endpoint compared to placebo, particularly for the opicapone 50 mg and 25 mg groups. This was in contrast to essentially no difference for entacapone compared to placebo in either of these assessments. The p-values for the comparisons between opicapone and entacapone indicate a significant difference favouring the opicapone 50 mg group.

The UPDRS, PDSS, PDQ-39, and NMSS showed slight improvements across all treatment groups, with no significant differences between them.

Safety results:

About half of the subjects in each treatment group experienced at least 1 TEAE. The highest incidence of TEAEs was reported for the entacapone group (56.6%), compared to 51.6% to 54.6% for the opicapone groups and 49.6% for placebo. The TEAEs occurring with a higher frequency in the opicapone groups compared to the placebo group (>2% difference) were dyskinesia (12.4% vs. 4.1%), insomnia (4.5% vs. 0.8%), and dizziness (3.1% vs. 0.8%). Compared to entacapone, the profile of TEAEs was similar, with dyskinesia being slightly more common in opicapone (12.4% vs. 8.2%), while nausea and falls were slightly more common with entacapone (nausea: 6.6% vs. 2.2%; falls: 4.1% vs. 2.0%). There was no apparent dose-relationship for the majority of TEAEs with opicapone.

The proportion of subjects with TEAEs considered to be related to IMP by the Investigator was 24.0% in the placebo group, 27.9% to 32.2% in the opicapone groups, and 33.6% in the entacapone group. Dyskinesia was the most frequently reported possibly related TEAE in all treatment groups with the highest incidence in the opicapone groups (13.1% in the 5 mg group, 7.6% in the 25 mg group, and 14.8% in the 50 mg group) compared to 7.4% for entacapone and 4.1% for placebo. No deaths were reported. Fewer opicapone subjects

(≤3.5% in any group) than either placebo (5.0%) or entacapone subjects (6.6%) reported treatment-emergent serious AEs.

The percentage of subjects who discontinued IMP due to a TEAE was similar across the treatment groups, with the lowest incidence in the opicapone 50 mg group (4.3%). The most common TEAEs leading to discontinuation were diarrhoea (1.6% entacapone, 0.8% placebo, no cases for opicapone), hallucinations (1.4% for opicapone, no cases for entacapone or placebo) and dyskinesia (0.6% for opicapone, no cases for entacapone or placebo).

For laboratory parameters there were no substantial changes across visits for any treatment group. The incidence of clinically significant or markedly abnormal values was comparable for all groups. For liver function tests, no issues of concern were observed for any of the opicapone groups or entacapone.

There were no relevant differences between treatment groups for changes from baseline in vital signs, or physical and neurological examinations.

Overall, no relevant trends or changes were noted over time or between treatment groups for the centrally read ECG parameters (axis, heart rate, PR interval, QRS interval, QT interval, QT interval corrected for heart rate using Bazett's formula [QTcB], QT interval corrected for heart rate using Fridericia's formula [QTcF], or RR interval).

There was no indication of an increased suicidality in the opicapone groups or entacapone group compared to placebo. Impulsive disorders were comparable in opicapone groups and entacapone and slightly more common than in placebo.

Summary:

Opicapone was effective at reducing OFF-time in PD patients with motor fluctuations. The opicapone 50 mg group met the primary efficacy objective to demonstrate superiority to placebo and non-inferiority to entacapone based on the change in OFF-time from baseline to endpoint of the DB period. This was confirmed by analyses of secondary efficacy variables: the proportion of OFF-time and ON-time responders at endpoint and the change from baseline to endpoint in OFF- and ON-time percentages, and improvements reported by the Investigator's and Subject's Global Assessments of Change. The opicapone safety and tolerability profile was favourable compared to entacapone indicating an overall positive risk-benefit for the use of opicapone in PD patients with motor fluctuations.

Date of final report:

27-Aug-2014