2 STUDY 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 (Part II - open-label extension phase).

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

Clinical phase: III

Reporting period: Open-label (OL) phase only

Study duration and dates: The duration per subject was up 52 weeks of the OL period and 2 weeks of the safety Follow-up.

Objectives: The objective of the OL phase of the study was to investigate the safety, tolerability, and maintenance of therapeutic effect of opicapone (5 mg, 25 mg, or 50 mg once daily [QD]) adjusted according to clinical response over 52 weeks of treatment, when administered with the existing treatment of levodopa (L-DOPA) plus a DDCI, in Parkinson's disease patients with end-of-dose motor fluctuations who completed the double-blind (DB) phase (Part I) of the study.

Methodology:

The OL phase of this study is a continuation of a Phase III, multicentre, double-blind (DB), randomised, placebo- and active-controlled, parallel-group study conducted in adults diagnosed with idiopathic Parkinson's disease and motor fluctuations. The study consisted of the following periods:

- A Screening period of up to 2 weeks.
- A DB period (DB treatment period of the DB phase) of 14 to 15 weeks.
- An OL period (OL treatment period of the OL phase) of 52 weeks.
- A Follow-up period of approximately 2 weeks.

The Screening and DB periods comprised the DB phase (Part I) of the study; the OL period and safety Follow-up period (for those subjects continuing into the OL period) comprised the OL phase (Part II). In the following, only the procedures and results related to the OL phase of the study are described. Details and results of the DB phase have been reported separately and are not included in this report.

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.

At the end of the DB period, subjects were eligible to enter an additional 52-week, OL period, in which all subjects were to be treated with opicapone (5 mg, 25 mg, or 50 mg). The OL period started on the day of the first intake of OL investigational medicinal product (IMP), which was defined as the day of V7, and ended at V14 (End-of-study [EOS], after approximately 52 weeks of OL treatment) or Early Discontinuation Visit (EDV). All subjects were to begin OL treatment at a dose of 25 mg/day opicapone for the first week (until V8). Thereafter, the opicapone and L-DOPA/DDCI doses could be adjusted according to clinical response, except from V13 to V14 (the end of the OL period), when L-DOPA and opicapone doses were to remain stable. The IMP was administered with existing treatment of L-DOPA/DDCI.

Number of subjects:

A total of 495 subjects were enrolled in the OL phase. Of these, 99 subjects had been treated with placebo in the DB phase, 100 with entacapone, 100 with opicapone 5 mg, 98 with opicapone 25 mg, and 98 with opicapone 50 mg.

Diagnosis and main criteria for inclusion:

Subjects were included in the study if they completed the DB phase of the study.

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

The IMP to be tested in this study was opicapone. There were no reference products in the OL phase of this study. 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, 110831, 120025, 120026, 120027, 120028, 120451, 120452, 120709, 120710).

Duration of treatment:

The total duration of OL treatment for an individual subject was up to 52 weeks.

Criteria for evaluation:

Efficacy: The following variables were obtained from subject's diary data at the different visits of the OL period and at endpoint:

- OFF-time.
- ON-time.
  - Total ON-time.
  - ON-time without dyskinesia (note: this is synonymous with the term "ON-time without any dyskinesia", which is used in the source documents).

- ON-time without troublesome dyskinesia.
- ON-time with non-troublesome dyskinesia.
- ON-time with troublesome dyskinesia.

The absolute OFF-/ON-times were calculated in minutes as the average of the daily sum of the 30-minute periods classified as ON (any state) or OFF in subject's diary. Percentage OFF-/ON-time at each visit and at endpoint was to be calculated as the absolute OFF-/ON-time, divided by the total time awake (calculated as the addition of all 30-minute periods in a given day where the subject had recorded any state other than Asleep), based on the information provided in the same diaries used for the calculation of absolute OFF-/ON-time.

In addition, OFF-/ON-time responders were assessed according to the following cut-off points:

- 1, 1.5, 2, and 2.5 hours reduction in OFF-time from DB baseline and OL baseline compared to endpoint.
- 1, 1.5, 2, and 2.5 hours increase in ON-time from DB baseline and OL baseline compared to endpoint.

The number of times a subject transitioned from ON (any state) to OFF each day was also counted. The average number of transitions per subject and day over the 3-day diary collection period preceding each visit was calculated.

Additional 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 including lipid panel, urinalysis), vital signs (blood pressure, heart rate), 12-lead electrocardiogram (ECG), physical and neurological examinations, the Columbia Suicide Severity Rating Scale (C-SSRS), and the Modified Minnesota Impulsive Disorders Interview (mMIDI).

Statistical methods:

Efficacy analysis:

Efficacy data for the OL period were generally summarised using descriptive statistics for the different variables at the different visits of the OL period, with respective changes from DB and OL baselines.

The course of the efficacy variables during both the DB and OL phases was used to evaluate the maintenance of the effect for subjects already treated with opicapone in the DB phase, and the effect of switching treatments for subjects treated with placebo or entacapone in the DB phase.

Each of the OFF- and ON-time variables were analysed using summary statistics (absolute [minutes] and percentage [relative to the total time awake]) by visit and the change from DB baseline and OL baseline.

In addition, the change in absolute OFF-time was analysed using several mixed models for repeated measurements (MMRM) to assess the time course of OFF-time during the DB and OL periods of the study, and an additional treatment effect after switching treatment. Estimated mean values (marginal means estimated from each of the MMRM models) of OFF-time by visit and DB treatment, estimated standard error, 95% confidence intervals of estimates, and p-values of DB treatment vs. placebo and entacapone are presented.

For the UPDRS, PDSS, PDQ-39, and NMSS questionnaires, summary statistics are presented for the absolute values and, if applicable, change from DB baseline and from OL baseline.

Safety analysis:

All safety analyses were analysed descriptively and presented for the OL-Safety Set (OL-SAF) for data from the OL phase only. Observations from DB baseline were included where applicable. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.0. The analyses focused on treatment-emergent AEs (TEAEs) and were categorized by system organ class (SOC) and preferred term (PT). Serious TEAEs (TESAEs), TEAEs leading to death, and TEAEs resulting in discontinuation of IMP were tabulated using frequency tables. In addition, the effect of switching the OL opicapone dose from a different DB dose or treatment group was evaluated by assessing the TEAEs occurring in the first 4 weeks of the OL period and during the remainder of the OL phase, and by assessing the dyskinesias occurring at any time in the OL phase until the last IMP intake.

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 summarised. Frequency and shift tables were presented for clinically significant abnormalities according to the Investigator, and markedly abnormal values according to sponsor's pre-specified criteria.

Results:

Of the 495 subjects in the OL Enrolled Set, all subjects were included in the OL-SAF, 494 subjects (99.8%) in the OL Full Analysis Set (OL-FAS), and 465 subjects (93.9%) in the OL Per-protocol (OL-PP) Set, and 432 (87.3%) completed the study.

Demographics and baseline characteristics:

In the OL-SAF, 60.4% of subjects were male, the mean age was 63.7 years, 70.5% were younger than 70 years, and all subjects were Caucasian. At OL baseline, subjects had a mean disease duration of 7.7 years, were treated with L-DOPA for a mean of 6.1 years and were experiencing motor fluctuations for 2.6 years. Dyskinesia was present in 41.8% of subjects.

As expected, subjects presented with better disease outcomes at OL baseline compared to the DB baseline. At OL baseline, mean absolute OFF-time was 4.9 hours, compared to 6.5 hours at DB baseline. Most of the ON-time was ON-time without dyskinesia (9.7 hours).

Efficacy results:

In the OL-FAS, the OFF-/ON-time data from subject's diaries showed maintenance and even slight improvement of the therapeutic effect of opicapone over the 52-week OL study duration. At the end of the OL period, OFF-time had decreased by more than 2 hours (-126.9 minutes) relative to DB baseline and by an additional 33.8 minutes since the OL baseline. This was accompanied by an increase in total ON-time of 119.7 minutes relative to DB baseline. During the OL period, all of the increase in ON-time (32.0 minutes) was without dyskinesia, and there was even a decrease, although minimal, in the ON-time with non-troublesome (-3.6 minutes) and troublesome dyskinesia (-0.3 minutes).

In general, the greatest improvements in OFF-time and ON-time efficacy variables were observed in subjects that switched from DB placebo or DB entacapone to opicapone, while subjects who continued on opicapone maintained their benefit from the DB period. The switch from DB placebo and DB entacapone to opicapone led to a significant decrease in OFF-time of -64.9 minutes (95% confidence interval [CI]: -93.9, -35.9) and -39.3 minutes (95% CI: -67.6, -11.1), and a gain in ON-time without dyskinesia of 43.1 minutes (95% CI: 5.4, 80.7) and 45.7 minutes (95% CI: 8.9, 82.4), respectively. At the end of the OL period, OFF-time and ON-time LS means were comparable irrespective of DB treatment ($p>0.05$ for all comparisons).

At OL endpoint, 69.2% of subjects were OFF-time responders (at least 1 hour OFF-time reduction relative to DB baseline) and 67.0% were ON-time responders (at least 1 hour ON-time increase relative to DB baseline). Moreover, 55.1% of the subjects had an OFF-time reduction (50.0% had an ON-time increase) of at least 2 hours, and 44.9% of the OL-FAS had an OFF-time reduction (42.3% had an ON-time increase) of at least 2.5 hours from DB baseline.

Overall, the UPDRS, PDSS, PDQ-39, and NMSS scores at OL endpoint were unchanged compared to DB endpoint. The Investigator's and Subject's Global

Assessments of Change both showed higher proportions of subjects with improvements at OL endpoint relative to DB endpoint.

Safety results:

Overall, 68.1% of the subjects experienced at least 1 TEAE during the OL phase. Dopaminergic AEs or other Parkinson's disease symptoms were the most commonly reported TEAEs during the study. Dyskinesia was the most frequent TEAE (14.5% of the subjects), followed by drug effect decreased (12.1%), (worsening) Parkinson's disease (6.7%), back pain (4.6%), and insomnia (4.6%). The majority of TEAEs were mild (54.9%) to moderate (35.8%) in intensity 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 opicapone. Worsening parkinsonism was more commonly reported in the OL phase compared to the DB phase, but this is most likely due to disease progression rather than treatment. As was seen during the DB phase, the incidence of gastrointestinal disorders such as nausea and diarrhoea remained low (<1.5% of subjects).

The proportion of subjects with TEAEs considered to be related to the study drug by the Investigator was 35.8% during the OL phase. Dyskinesia was the most frequently reported possibly related TEAE in 13.1% of subjects.

Eleven deaths were reported during the OL phase, none of which were considered related to opicapone. Three cases were primarily due to respiratory tract infections (acute pneumopathy, possibly influenza-related death, and pneumonia), 2 due to cardiac disorders (cardiovascular insufficiency and myocardial infarction), 2 due to embolism (possible thromboembolism following appendectomy and pulmonary embolism secondary to prostate cancer), 2 due to cancer (metastatic cancer in spine and small cell lung cancer), 1 due to multi-organ failure after brain neoplasm surgery, and 1 due to sudden death.

Forty-eight (9.7%) subjects reported at least 1 TESAE during the OL phase, of whom 5 (1.0%) subjects experienced at least 1 possibly related TESAE. The TESAEs reported for >1 subject were intestinal obstruction and cauda equina syndrome (3 subjects each, 0.6%) and atrial fibrillation, bronchitis, ankle fracture, benign prostatic hyperplasia, basal cell carcinoma, malignant melanoma, sciatica, hypertension, and pneumonia (2 subjects each, 0.4%).

Few subjects (<7%) withdrew from the OL phase due to an AE. Dyskinesia (0.8%) was the most common TEAEs leading to discontinuation.

Few subjects reported cardiovascular or cerebrovascular TESAEs or skin cancers. There were no TESAEs related to hepatic toxicity.

There were no relevant changes in laboratory parameters, vital signs, physical or neurological examinations, or ECG readings. There was no indication of an increase in suicidality or in the incidence of impulsive disorders over the year of treatment with opicapone in the OL phase.

Summary:

Long-term use of opicapone for up to 52 weeks in the dose range of 5 mg to 50 mg was safe, well tolerated and provided sustained efficacy in reducing OFF-time and increasing ON-time in Parkinson's disease patients with motor fluctuations on L-DOPA therapy.

Date of final report:

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