2 SYNOPSIS

Name of Sponsor/Company: BIAL – Portela & Cª, SA	**Individual Study Table Referring to Part of the Dossier:**	***(For National Authority Use only)***
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Name of Active Ingredient: Nebicapone (BIA 3-202)	**Volume:** **Page:**	

Title of study:
A multicentre, double-blind, randomised, active- and placebo-controlled trial to investigate the efficacy and tolerability of nebicapone in Parkinson's disease patients with "wearing-off" phenomenon treated with levodopa/carbidopa or levodopa/benserazide

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Study centres: The study was conducted in 40 sites in Europe and South America: Argentina (6); Austria (2); Brazil (5); France (1); Hungary (4); Poland (7); Portugal (2); Romania (7); and Ukraine (6).

Publication (reference): Not yet published at time of preparation of this report.

Study period:		**Phase of development:**
First patient in:	26 September 2006	Phase II / therapeutic exploratory
Last patient out:	21 September 2007 (last patient, last visit)	

Objectives:
Primary objective: to investigate the effect on the "wearing-off" phenomenon of 3 different doses of nebicapone (NEB 50 mg, 100 mg and 150 mg), compared with entacapone and placebo when administered concomitantly with existing treatment with levodopa plus a dopa decarboxylase inhibitor (DDCI: carbidopa or benserazide).
Secondary objective: to investigate the safety and tolerability of the combined treatment (levodopa/DDCI plus nebicapone, entacapone or placebo).

Methodology:
Multicentre study with a screening visit (Visit V1), a single-blind placebo run-in period of 1 or 2 weeks (Period 1, Visits V2 to V3), and an 8-week randomised, double-blind, active- and placebo-controlled, parallel-group (5 groups) treatment period (Period 2, Visits V3 to V7). In Hungary only: a 1-week tapering-off period was added by amendment #1HU. The dosage of nebicapone was to be tapered off stepwise during 6 days. This period was to end with a follow-up Visit V8.

Number of patients (planned and analysed):
Planned: 250 (50 per treatment group)
Analysed:
Randomised: 254; Safety: 252; Intention-to-treat (ITT): 250; Per-protocol (PP): 215

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Diagnosis and main criteria for inclusion:
Male and female patients aged 30 to 80 years with idiopathic Parkinson's disease (modified Hoehn & Yahr less than Stage 5 during "off" time), who have been treated with levodopa/DDCI for at least 1 year with clear clinical improvement, whose treatment regimen (4 to 8 daily doses of standard levodopa/DDCI; other anti-Parkinson drugs) has been stable for at least 4 weeks before screening, who have exhibited signs of end-of-dose deterioration ("wearing-off" phenomenon) for a minimum of 2 months before screening, and who are able to keep reliable diaries of motor fluctuations.

Test product, dose (batch numbers) and mode of administration:
Nebicapone (BIA 3-202, NEB) was available as encapsulated tablets in 3 strengths: 50 mg (batch numbers 060004-L, 060106-L, 070151), 100 mg (060006-L, 060107-L, 070152) and 150 mg (060031-L, 060108-L, 070153). Patients took 1 capsule of investigational product orally with each dose of levodopa/DDCI.

Duration of treatment:
One or 2 weeks placebo run-in, 8 weeks (56 days) double-blind treatment. In Hungary, patients were to receive an additional 6 days (for a total of 62 days) of double-blind treatment in the tapering-off period.

Reference therapy, dose (batch numbers) and mode of administration:
Entacapone was available as encapsulated tablets in 200 mg strength (Novartis Comtan® batch numbers U0036, U0039 and U0044). The placebo was available as encapsulated tablets (batch numbers 060003-L, 060105-L and 070150). Patients took 1 capsule of entacapone 200 mg or placebo orally with each dose of levodopa/DDCI.

Criteria for evaluation:
Efficacy variables:
Primary endpoint: Change from baseline in absolute "off" time (from patient's diaries) at Visit V7 (end of the 8-week treatment period).
Secondary endpoints: Change from baseline and absolute values of absolute "off" time over the whole 8-week treatment period; percentage "off" time; number of uninterrupted "off" periods; percentage "on" time without troublesome dyskinesia; Unified Parkinson's Disease Rating Scale (UPDRS) I; UPDRS II at "off" stage; UPDRS III at "on" stage; UPDRS II plus III at "on" stage; item 39 of UPDRS IV; UPDRS V Modified Hoehn & Yahr Staging at "on" stage; UPDRS VI Schwab and England Activities of Daily Living Scale at "on" and "off" stage; modified Abnormal Involuntary Movement Scale (AIMS); proportion of different responder types; investigator's global assessment of change; patient's global assessment of change; and change in levodopa dose.
Safety variables:
Adverse events (AEs); clinical laboratory tests (haematology, biochemistry and urinalysis); vital signs (blood pressure, pulse rate, body weight); 12-lead electrocardiogram (ECG);

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physical/neurological examination; "on" time with troublesome dyskinesia; and complications of therapy, as assessed by UPDRS Section IV.

Statistical methods:

Primary efficacy analysis: Change from baseline in absolute "off" time until the end of the 8-week treatment period was compared between placebo and the NEB groups by an analysis of covariance (ANCOVA) with fixed effects treatment, region, treatment-by-region interaction and with the baseline value of absolute "off" time as covariate. Dunnett's multiple comparison procedure was used for the multiple comparisons of the NEB groups to the placebo group.

Secondary efficacy analyses:

The primary efficacy analysis as described above was repeated both with a different missing replacement algorithm and different covariates. Additionally, this analysis was carried out in the entacapone 200 mg group. Absolute "off" time, percentage "off" time, percentage "on" time without troublesome dyskinesia, and total scores of the modified AIMS at each visit over the 8-week treatment period were analysed using descriptive statistics. For all these variables except modified AIMS, a repeated-measures ANCOVA was performed in addition. Percentage "off" time, percentage "on" time without troublesome dyskinesia, and total scores of modified AIMS were also analysed by an ANCOVA at the end of the 8-week treatment period. Descriptive statistics were presented for the number of uninterrupted "off" periods. Proportions of responder types were analysed and compared between treatment groups by a Cochran-Mantel-Haenszel (CMH) test. For UPDRS, descriptive statistics were presented for total scores and treatment comparisons were made by the Kruskal-Wallis test. Additionally, for the single items of UPDRS and modified AIMS, the proportion of patients rated in each category at baseline and at the end of the 8-week treatment period was presented. Total daily dose of levodopa was summarised using descriptive statistics and was compared between treatment groups by the Kruskal-Wallis test. The proportion of patients with a change in levodopa dose compared to baseline was also presented. Descriptive statistics were presented for investigator's and patient's global assessment of change and treatment comparisons were made by a CMH test.

Safety analysis:

AEs were summarised by treatment group. All treatment-emergent adverse events (TEAEs) were summarised by calculating the number and proportion of patients with AEs by treatment group, preferred term and system organ class. Additionally, TEAEs were summarised by time to onset of AE, severity (intensity), seriousness and relationship to treatment. Brief written narratives were prepared describing each death, each serious AE, and for all patients who withdrew from the study because of AEs. Clinical laboratory variables and vital signs variables were summarised for each treatment group by calculating summary statistics on the actual values and on the change from baseline at key

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time points. The number and proportion of patients with values outside the limits of clinical significance were summarised. All values as well as the number of patients with clinical laboratory values outside the normal range were summarised in shift tables. For ECG, shift tables showing the number of patients with clinically relevant abnormal values were presented. UPDRS IV sub-scores and total score were summarised by treatment group and for items 32 and 33 the proportion of patients rated in each category at baseline and at the end of the 8-week treatment period was presented.

Summary – Conclusions:

Efficacy results

NEB 150 mg was the most effective NEB dose. In the primary analysis (intention-to-treat [ITT] population), this dose produced a significantly greater reduction in absolute "off" time at Visit V7 than placebo. In the other NEB groups, treatment effects on absolute "off" time at Visit V7 were markedly smaller and not significantly different from the effect observed for placebo.

ANCOVA results for change in absolute "off" time (minutes) from baseline to Visit V7 – ITT population (LOCF applied): Nebicapone vs. placebo

	Placebo (N=49)	NEB 50 mg (N=53)	NEB 100 mg (N=52)	NEB 150 mg (N=46)
Absolute values				
Least squares mean	–35	–58	–75	–142
Standard error	24.2	23.1	23.8	26.7
95% confidence interval	–83; 12	–104; –13	–122; –28	–194; –89
Comparison to placebo				
Least squares mean	–	–23	–39	–106
Standard error	–	33.4	34.0	36.0
95% confidence interval [a]	–	–102; 56	–120; 41	–192; –21
p-value [a]	–	0.8353	0.5159	0.0101

[a] Adjusted for multiple testing according to Dunnett's procedure.
Source: Section 15.2, Table 15.2.1.1

NEB 150 mg was also significantly more effective than placebo in nearly all secondary analyses in the ITT population.

Effects for NEB 100 mg, NEB 50 mg and entacapone 200 mg in the ITT population were generally greater than those for placebo, but the differences to placebo were statistically significant only in some cases.

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The results of analyses of diary data in the per-protocol (PP) population were similar to those in the ITT population in all active treatment groups. However, due to a larger effect in the placebo group, treatment differences were smaller in the PP population. For other efficacy analyses, no notable differences were found between the PP and ITT populations. Results were consistent across the different analyses.

Safety results

The overall frequency of TEAEs varied between about 30% and 50% across the treatment groups, but no dose relationship was observed in the NEB groups. The highest overall frequency of TEAEs was observed in the NEB 100 mg group (49%).

The most frequent types of TEAE were gastrointestinal disorders, investigations, nervous system disorders, and psychiatric disorders. For gastrointestinal, nervous system, and psychiatric disorders, the frequency of TEAEs was highest in the NEB 100 mg group. Investigations were most frequent in the NEB 150 mg group. The most frequent individual TEAEs were diarrhoea, headache, nausea, and urine colour abnormal. For these 4 TEAEs, the differences in frequency between treatment groups were small. Only abnormal urine colour occurred in all treatment groups, including placebo. The vast majority of TEAEs were classified as mild or moderate. Most patients recovered without sequelae by the end of the study.

The frequency of serious TEAEs was low (5 patients with 6 TEAEs: diabetic neuropathy in 1 NEB 100 mg patient; diarrhoea and hepatic enzyme increased in 1 NEB 150 mg patient; transaminases increased in 1 NEB 150 mg patient; prostate cancer in 1 NEB 150 mg patient; dyskinesia in 1 entacapone 200 mg group patient). No patients experienced a TEAE that resulted in death. The frequency of TEAEs leading to withdrawal was comparable in all treatment groups (4.0-7.5%), except for the NEB 50 mg group where only 1 patient withdrew due to a TEAE.

No relevant treatment differences were observed for any of the haematology variables investigated. Changes in the liver function tests (aspartate and alanine transaminases, AST and ALT, respectively) from normal to high were more frequent in all NEB groups than in the placebo group, but no dose relationship was discernible. Clinically relevant elevations in AST and/or ALT were observed in the highest NEB dose group NEB 150 mg (4 of 46 patients [9%]); these findings were also reported as TEAEs. In 2 of the 4 cases, the TEAE was serious, and in 1 other case, the TEAE led to withdrawal from study. No clinically relevant elevations in AST or ALT occurred in any of the other treatment groups.

No relevant differences were detected between nebicapone and placebo in other safety analyses.

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Conclusion The results of this study show that NEB 150 mg is highly efficacious but poorly tolerated by the liver. The NEB 100 mg and NEB 50 mg doses were less efficacious with effects being significantly different from placebo only in some secondary variables.		
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