2. SYNOPSIS

Name of Sponsor/Company: Impax Pharmaceuticals, a Division of Impax Laboratories, Inc	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: IPX066		
Name of Active Ingredient: Carbidopa-Levodopa		

Title of Study: A Placebo-Controlled Study to Evaluate the Safety and Efficacy of IPX066 in Subjects with Parkinson's Disease

Principal Investigator:
Rajesh Pahwa, MD, Professor of Neurology, Landon Center on Aging, University of Kansas Medical Center, Department of Neurology, Parkinson's Disease Center, Kansas City, Kansas, USA
Investigators: 56 Investigators

Study center(s):
56 sites in North America (United States and Canada) and Europe (Ukraine, Romania, Lithuania, Latvia, Estonia)

Publications (Abstracts):
Pahwa R, Hauser R, Jankovic J, Nausieda P, Ellenbogen A, Clinical Team of Impax Pharmaceuticals. Double-Blind, Placebo-Controlled Fixed-Dose Trial of IPX066, a Novel Carbidopa-Levodopa (CD-LD) Extended-Release Formulation, in Early Parkinson's Disease (APEX-PD Trial). American Academy of Neurology 63rd Annual Meeting, Hawaii, USA.
Pahwa R, Ellenbogen A, Jankovic J, Hauser, R, Fahn S, Clinical Team of Impax Pharmaceuticals. Efficacy and Safety of IPX066, a New Carbiodpa-Levodopa (CD-LD) Extended-Release Formulation, in LD-naïve Early Parkinson's Disease (APEX-PD Trial). 15th International Congress of Parkinson's Disease and Movement Disorders, June 2011, Toronto, Canada.

Studied period (years):	**Phase of development:**
Date first patient enrolled: 13 April 2009 Date last patient completed: 5 October 2010	3

Objectives:
The objective of this study was to evaluate the safety and efficacy of IPX066 in the treatment of subjects with early Parkinson's disease (PD). An additional objective was to evaluate the impact of IPX066 on the quality of life in subjects with early PD.

Methodology:
This phase 3, randomized, double-blind, placebo-controlled, fixed-dose, parallel-arm study evaluated three doses of IPX066 versus placebo in the treatment of subjects with early PD who had not previously been treated with levodopa (LD) or catechol-O-methyl transferase (COMT) inhibitors for more than 30 days and not within 4 weeks before study enrollment (i.e., subjects who were considered LD naïve) and were not treated with dopamine agonists. IPX066 is an extended-release capsule formulation of carbidopa–levodopa (CD–LD) in a 1:4 ratio. Subjects were equally randomized into one of four treatment groups:

IPX066 36.25–145 mg CD–LD (referred to as 145 mg LD)

IPX066 61.25-245 mg CD–LD (referred to as 245 mg LD)
IPX066 97.50–390 mg CD–LD (referred to as 390 mg LD)
Matching placebo

This 30-week study included a Titration period of 4 weeks (up to 3 weeks of dose escalation and 1 week of stabilization), which allowed escalation to the assigned dose, and a 26-week Maintenance treatment period. The primary efficacy outcome measure was change from Baseline in the sum of United Parkinson's Disease Rating Scale (UPDRS) Part II and Part III scores at the End of Study (i.e., Week 30 or the last post-Baseline value reported if the subject discontinued the study prematurely).

Number of subjects (planned and analyzed):

Planned: 350 subjects, to achieve approximately 75 subjects in each of 4 treatment groups at study completion.

Actual: 381 subjects randomized (87 in the 145 mg LD group, 104 in the 245 mg LD group, 98 in the 390 mg LD group, and 92 in the placebo group).

Diagnosis and main criteria for inclusion:

Eligible male and female subjects were at least 30 years of age at the time of idiopathic PD diagnosis, which was based on the United Kingdom PD Society Brain Bank Diagnostic Criteria, and were LD naïve. Subjects must also have met the following evaluation requirements: the sum of the UPDRS Part II plus Part III score was ≥ 18 at Screening and Baseline Visits; Mini-Mental State Examination (MMSE) score was ≥ 26 at screening; and PD was Hoehn and Yahr Stage I, II, or III. Subjects who had used dopamine agonists within 30 days before Screening were excluded.

Subjects taking anticholinergics, amantadine, or monoamine oxidase type B (MAO-B) inhibitors were to maintain a stable regimen for at least 4 weeks before Baseline and throughout the study. All subjects provided written consent before screening procedures were initiated.

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

The investigational product was IPX066, an extended-release (ER) multiparticulate, capsule formulation of CD and LD in a 1:4 ratio. IPX066 was provided in four dosage strengths from the corresponding lots:

IPX066, 23.75–95 mg CD–LD (referred to as the 95 mg LD)—Lot PB00209.
IPX066, 36.25–145 mg CD–LD—Lot RB09012.
IPX066, 48.75–195 mg CD–LD—Lot RB09011.
IPX066, 61.25–245 mg CD–LD—Lot RB09010.
Subjects receiving 97.50-390 mg CD–LD received two capsules of 195 mg LD per dose.

Subjects were randomized to one of the following four treatment groups:

IPX066
145 mg LD dosed 3 times daily (total daily dose of 435 mg LD)
245 mg LD dosed 3 times daily (total daily dose of 735 mg LD)
390 mg LD (2 × 195 mg LD) dosed 3 times daily (total daily dose of 1170 mg LD)
Placebo dosed 3 times daily

During the first 4 weeks of the study, subjects followed a specific dose-titration schedule based on the treatment to which they were randomized such that at the end of the Titration period, all subjects were receiving their assigned fixed dose. Subjects received one capsule per dose Days 1 through Day 21. The 145 mg and 245 mg dose groups reached their respective assigned dose on Day 4 and 15, respectively. Starting on Day 22, the day all subjects were at their randomized dose, subjects received two capsules per dose. During the following 26-week Maintenance treatment period, subjects remained on their assigned dose.

Duration of treatment:

This 30-week double-blind study included a 4-week Titration period and a 26-week Maintenance

treatment period.

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

Reference therapy was 2 placebo capsules administered 3 times daily.

For blinding purposes, placebo capsules were provided in identical, size 00, gray capsules as the active capsules. The placebo capsules contained sugar spheres and microcrystalline cellulose. Placebo lots: RB0802 and RB09006.

Criteria for evaluation:

Efficacy

Primary efficacy:

- Primary efficacy endpoint—Change from Baseline in the UPDRS Questionnaire Part II plus Part III score at the End of Study (i.e., the value obtained at Week 30 or the last post-Baseline value reported if the subject discontinued the study prematurely).

Secondary efficacy:

- Sum of individual UPDRS Parts, sum of UPDRS Parts I through III, and sum of UPDRS Parts I through IV collected at Visits 2, 3, 4, 5, and 6 and End of Study and sum of UPDRS Parts II and III collected at Visits 2, 3, 4, 5, and 6.
- Patient Global Impression (PGI) score at End of Study and at Visits 2, 3, 4, 5, and 6 (Weeks 4, 9, 16, 23, and 30).
- Clinical Global Impression (CGI) score at End of Study and at Visits 2, 3, 4, 5, and 6 (Weeks 4, 9, 16, 23, and 30).

Quality of Life

- Parkinson's Disease Questionnaire 39 (PDQ-39)—Change from Baseline in the PDQ-39 at End of Study and at Visits 2, 3, 4, 5, and 6 (Weeks 4, 9, 16, 23, and 30).

Safety

- Treatment-emergent adverse events (AEs), actively solicited and collected as reported by the subject throughout the study.
- Concomitant medications throughout the study.
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate) at Screening, Baseline, Weeks 4, 9, 16, 23, and 30 or early discontinuation.
- Electrocardiograms (ECGs, 12 lead) at Screening, Week 16, and Week 30 or early discontinuation.
- Clinical safety laboratory tests at Screening, Week 16, and Week 30 or early discontinuation.
- Beck Depression Inventory-II (BDI-II) at Screening and at Week 30 or early discontinuation.

Statistical methods:

Efficacy

Subjects were equally randomized into the four treatment groups within each of two strata:

- Stratum 1–Subjects who had never taken PD medications
- Stratum 2–Subjects who had previously taken or were using allowed non-LD medications for PD.

All treated subjects with at least one efficacy measurement after dosing were included in the efficacy analyses. Data from subjects who withdrew before completing 30 weeks of treatment were included in the analyses at the End of Study, using a last observation carried forward (LOCF) approach.

The primary outcome was analyzed assuming a three-factor model with treatment, stratum, and center being the factors.

For continuous secondary endpoint variables (sum of UPDRS Parts II–III, Parts I–III, and Parts I–IV, and the QOL endpoint PDQ-39 as a function of time), similar analyses were conducted. By definition, CGI and PGI encompass change, so no Baseline adjustment was necessary. Categorical variables were examined using Cochran-Mantel-Haenzel chi-squared techniques.

Safety

All randomized subjects who received at least one dose of study medication were included in the safety analysis. Reported AEs were coded to standard terms using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.1.

Treatment-emergent AEs were tabulated, as were laboratory test data, findings of physical examinations, vital signs, ECG results, BDI-II scores, and concomitant medications. Treatment-emergent AEs were defined as AEs that started after the first dose of study treatment was administered or within 72 hours after the last dose of study treatment was administered; this was done because subjects were likely to alter their dopaminergic medications soon after discontinuing study treatment. No hypothesis testing was performed on the safety data. For completeness, AEs that occurred at anytime during the study are included in the posttext listings.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Demographics: Baseline demographics were well-balanced across the four treatment groups. The average age of subjects ranged between 63.8 and 65.4 years, slightly more than one-half of the subjects were male (mean, range 54.0% to 56.7%), almost all subjects were white (mean, range 97.8% to 100%), and the vast majority of subjects were not of Hispanic or Latino ethnicity (mean, range 87.5% to 94.6%). Overall, the mean age at PD onset was 63 years, and the mean duration of PD at study entry was 1.98 years. The majority of subjects (67.6%) had Hoehn and Yahr Stage II PD at Baseline. The UPDRS Part II plus Part III score for most subjects was between 20 and < 50 units (79.8%). Overall, there were no statistically significant differences in the distribution of the total PDQ-39 scores at Baseline across the treatment groups.

UPDRS Results: At the End of Study (EOS), 361 subjects were available for analysis of efficacy. Overall, the change from Baseline in the UPDRS Part II plus Part III score was statistically significant for each of the three IPX066 treatments compared to placebo ($P < 0.0001$). The mean improvement from Baseline for each of the IPX066 treatments (145 mg LD, 245 mg LD, and 390 mg LD) was 11.7, 12.9, and 14.9 units, respectively, compared with a mean improvement of a 0.6 unit for placebo. The results were similar ($P \leq 0.0001$) for each of the IPX066 treatments compared with placebo at Weeks 4, 9, 16, 23, and 30, indicating that the treatment effect was evident from the first post-Baseline visit (Week 4) and was sustained to EOS. While there were no statistically significant differences among the active treatments, the IPX066 390 mg LD group had the greatest improvement in URPDS score.

A responder analysis (with a responder defined as a subject who improved at least 5 units from Baseline in the UPDRS Part II plus Part III score) demonstrated that each of the IPX066 treatments was statistically significantly superior to placebo (all $P < 0.0001$) at the EOS with response rates ranging from 70.1% to 79.8% for the active treatments compared to 30.4% for placebo.

Patient Global Impression: Subjects gave their impression of the treatment received since the start of treatment using a 7-point scale ranging from 1 (Very Much Worse) to 7 (Very Much Better) with a score of 4 being No Change. At the EOS, each of the three active treatments was statistically significantly superior to placebo ($P < 0.0001$). The percent of subjects reporting improvement ranged from 70.3% to 73.5% for the active treatments compared to 33.7% for placebo.

Clinical Global Impression: Clinicians provided an assessment using the same scale as the subjects. At the EOS, each of the IPX066 treatments was statistically significantly superior to placebo ($P < 0.0001$). The percent of clinical reports of improvement ranged from 70.8% to 72.6% for the active treatments compared to 27.2% for placebo.

Quality of Life PDQ-39: At the EOS, each of the three IPX066 treatments was statistically significantly superior to placebo (IPX066 145 mg LD, $P = 0.0173$; 245 mg LD, $P = 0.0332$; and 390 mg LD, $P = 0.0008$).

SAFETY RESULTS:

More than two-thirds (68.5%) of the 381 subjects evaluable for safety experienced AEs, and the AE rate in the 145 mg LD group (56.3%) was notably lower than that of the placebo group (72.8%) and the

245 mg LD (72.1%) and 390 mg LD (71.4%) groups.

The most common AEs (i.e., occurring in >10% of subjects) also occurred less frequently in the placebo and 145 mg LD groups than in the 245 mg LD and 390 mg LD groups, respectively: nausea (8.7% and 13.8% compared with 19.2%, and 20.4%), headache (10.9% and 6.9% compared with 12.5%, and 17.3%), and dizziness (5.4% and 9.2% compared with 19.2% and 12.2%). Other AEs occurring in >5% of subjects that were reported more often in at least one of the IPX066 treatment groups than in the placebo group included insomnia, abnormal dreams, dry mouth, vomiting, constipation, dyskinesia, anxiety, and orthostatic hypotension. Aside from depression, which occurred in a higher proportion of subjects in the placebo group than in the IPX066 groups, most of these AEs clustered in the two higher IPX066 dose groups.

The overall treatment-related AE rates in the 145 mg LD group (43.7%) and the placebo group (47.8%) were similar and lower than those in the 245 mg LD (54.8%) and 390 mg LD (59.2%) groups. Few subjects reported AEs with a maximal intensity of severe (2.3% and 1.1% in the 145 mg LD and placebo groups and 6.7% and 5.1% in the 245 mg LD and 390 mg LD groups, respectively).

None of the 14 SAEs that occurred were related to study treatment, and the numbers of subjects experiencing SAEs were similar across all treatment groups: 4 subjects (4.6%) in the 145 mg LD group (1 each of coronary artery disease, myocardial infarction, urinary tract infection, and acute myocardial infarction); 5 subjects (4.8%) in the 245 mg LD group (1 each of coronary artery bypass, complete atrioventricular block, osteoarthritis, abdominal strangulated hernia, and non-Hodgkin's lymphoma), and 2 subjects (2.0%) in the 390 mg LD group (1 with urinary tract infection and 1 with COPD and emphysema) compared with 3 subjects (3.3%) in the placebo group (1 each of urosepsis, cerebrovascular accident, prostatectomy). One death (Subject 209-006, randomized to the 245 mg LD group) that was attributed to non-Hodgkin's lymphoma occurred during the Titration period.

Overall, 39 subjects (10.2%) experienced AEs that contributed to early discontinuation of treatment, with a smaller percentage of subjects in the 145 mg LD and placebo groups (5.7% and 4.3%, respectively) than in the 245 mg LD and 390 mg LD groups (14.4% and 15.3%, respectively.).

Differences among the treatment groups in laboratory test results and vital signs were unremarkable. There were no clinically meaningful differences in the distribution of subjects by QTcF intervals across any of the treatment groups and time points.

CONCLUSIONS:

The following conclusions are based on the efficacy results observed in Study IPX066-B08-05:

- All three IPX066 treatments were statistically significantly superior to placebo on the primary measure of change from Baseline in the UPDRS Part II plus Part III score at the EOS. A treatment effect was seen as early as the first post-Baseline assessment (Week 4) and continued for the duration of the study (Week 30). Results obtained using other UPDRS subscales and combinations supported the findings of the primary measure.
- The responder analysis supported the findings that each of the IPX066 treatments was statistically significantly superior to placebo at the EOS.
- The independent secondary endpoints of PGI and CGI endpoints were also statistically significantly superior to placebo at the EOS.
- Results of the quality-of-life measure PDQ-39 also supported the demonstrated efficacy of the three IPX066 treatments noted with the UPDRS and the PGI and CGI.

The following conclusions are based on the safety results observed in Study IPX066-B08-05:

- The most frequent AEs (>5% in any treatment group) reported in the IPX066 treatment groups represent typical dopaminergic effects: nausea, vomiting, constipation, dry mouth,

headache, dizziness, insomnia, abnormal dreams, dyskinesia, anxiety, and orthostatic hypotension.

- The overall AE rate in the IPX066 145 mg LD dose group was the lowest compared with the higher IPX066 dose groups and the placebo group. The incidence of dopaminergic side effects, such as nausea, dizziness, dyskinesia, hallucinations, insomnia, and abnormal dreams, were higher in the two higher IPX066 dose groups.
- There were no treatment-related SAEs, and the SAE rates were similar across all treatment groups.
- AEs contributed to early discontinuation in more subjects in the two higher IPX066 dose groups than in the lowest IPX066 dose group and the placebo group.
- While individual laboratory abnormalities were noted, there were no trends or dose relationship in clinically significant laboratory or ECG abnormalities.

Overall, the results from this double-blind, placebo-controlled, fixed-dose study indicate that all three doses of IPX066 included in the study were well tolerated and efficacious in subjects with early PD. Among the three IPX066 doses, the 145 mg LD appeared to have a better tolerability profile.

Date of the report: 10 October 2011