2 STUDY SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
KYOWA HAKKO UK Ltd
258 Bath Road, Slough
Berkshire SL1 4DX, United Kingdom</td><td rowspan="3">Individual Study table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
Istradefylline</td></tr>
<tr><td>Name of Active Ingredient:
(E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione</td></tr>
<tr><td colspan="3">Title of Study:
A 16-week, Double-Blind, Placebo-Controlled, Randomised, Parallel-Group, Multicentre, International Study to Evaluate the Efficacy and Safety of 40 mg/day KW-6002 (istradefylline) and that of Entacapone versus Placebo as Treatment for Parkinson's Disease in Patients with Motor Response Complications on Levodopa[a] Therapy</td></tr>
<tr><td colspan="3">Investigators:
Argentina: Drs R Femminini, G Saredo, N Garretto*, M Merello, H Zezza, O Gershanik; Austria: Prof W Poewe; Chile: Drs D Saez, M Leiva, C Kunstmann; Estonia: Drs P Taba; K Gross-Paju, H Nurm; France: Prof O Rascol; India: Drs M Bhatt, R Borgohain, A Shah, R Srinivasa, R Shukla, A Kishore, S Prabhakar; Italy: Prof F Stocchi, Drs U Bonuccelli, M Onofrj, Prof G Meco; Latvia: Drs. I Bluma, E Vitols; Lithuania: Drs D Obelieniene, I Bickuviene; Russia: Drs G Avakyan, N Fedorova, A Skoromets, M Odinak, I Stoliarov, E Iakoupov, S Iliarioshkin; Republic of South Africa: Drs FH Badenhorst, C Coetzee, J Green, D Lurie, J Smuts, F Verster, M Isaacs, Prof BM Kies, Dr J Carr; Spain: Drs J Kulisevsky Bojarski, J Lopez Lozano, J Martinez Castrillo, A Castro Garcia; United Kingdom (UK): Drs D Burn, R Barker, B Wood; Ukraine: Profs I Karaban, T Mishchenko, Dr S Moskovko, Prof Y Golovchenko.
* Replaced Dr Bueri.</td></tr>
<tr><td colspan="3">Study Centers: A total of 56 centers: Argentina (6); Austria (1); Chile (3); Estonia (3); France (1); India (7); Italy (4); Latvia (2); Lithuania (2); Russia (7); Republic of South Africa (9); Spain (4); United Kingdom (3); Ukraine (4).</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Studied Period: 24 November 2004 (Date of First Dose) to 03 October 2005 (Date of Last Dose)</td><td>Clinical Phase: Phase 3</td></tr>
<tr><td colspan="3">Objectives:
<u>Primary Objective</u>: The primary objective of this study was to establish the efficacy of 40 mg/day istradefylline in reducing the percentage of awake time per day spent in the OFF state in subjects with Parkinson's disease treated with levodopa.
<u>Secondary Objectives</u>: The secondary objectives of this study were to evaluate:
• The efficacy of a 40 mg/day dose of istradefylline for reducing the total hours of OFF time;
• The change in total hours and percentage of ON time without dyskinesia, with dyskinesia, with non-troublesome dyskinesia, with troublesome dyskinesia, and without troublesome dyskinesia;
• The change in Unified Parkinson's Disease Rating Scale (UPDRS) Subscales I (Mentation, Behavior and Mood), II (Activities of Daily Living), III (Motor Examination), and IVA (Dyskinesia) scores;
• The change in the Parkinson's Disease Questionnaire (PDQ-39 and PDQ-8) and Medical Outcomes Study 36-item Short Form (SF-36);
• The Patient Global Impression - Improvement scale (PGI-I);</td></tr>
</table>

[a] Refers throughout this report to levodopa in combination with either benserazide or carbidopa with or without additional anti-parkinsonian concomitant drugs

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Secondary Objectives *(continued)*:

- The change in the Clinical Global Impression - Severity of Illness scale (CGI-S); and
- The safety of a 40 mg/day dose of istradefylline by evaluation of changes in safety parameters.

Methodology: This was a 16-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter, international study designed to evaluate the efficacy and safety of istradefylline compared with placebo and the efficacy and safety of entacapone compared with placebo in approximately 405 subjects with Parkinson's disease and motor response complications while receiving levodopa therapy. After giving informed consent, subjects underwent a 2- to 3-week screening and baseline period during which they were assessed for eligibility. Eligible subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups:

- istradefylline 40 mg/day given with the first daily dose of levodopa followed by placebo with subsequent doses of levodopa;
- entacapone 200 mg to be given with every dose of levodopa; or
- placebo to be given with every dose of levodopa.

Following randomization to double-blind treatment, subjects entered an initial 4-week period during which their levodopa dose may have been adjusted to an optimal level if required; however, the frequency of dosing could not have been changed. Subjects then entered a 12-week period during which adjustments to the levodopa-dosing regimen were considered protocol deviations. Efficacy was evaluated by the 24-hour ON/OFF patient diary, UPDRS, CGI-S, PDQ-39, SF-36, and PGI-I scales, and safety was assessed by physical examinations (including neurological examinations), clinical laboratory tests, 12-lead ECGs, vital signs, body weight, adverse events, and concomitant medications.

Subject Population:

Number of Subjects Planned: Planned: 405 (135 per treatment arm)

Number of Subject Randomized: 464: 159 in the istradefylline group, 153 in the entacapone group, and 152 in the placebo group.

Number of Subjects Evaluated for Efficacy: 455 (intent-to-treat [ITT]): 158 in the istradefylline group, 146 in the entacapone group, and 151 in the placebo group; 390 (per-protocol analysis set): 141 in the istradefylline group, 124 in the entacapone group, and 125 in the placebo group.

Number of Subjects Evaluated for Safety: 464 (safety analysis set): 159 in the istradefylline group, 153 in the entacapone group, and 152 in the placebo group.

Diagnosis and Main Criteria for Inclusion: Subjects randomized to receive study drug were male or female, at least 30 years of age, met United Kingdom's Parkinson's Disease Society brain bank criteria (Step 1 and Step 2) for Parkinson's disease and the severity of the Parkinson's disease was defined as Stages 2-4 on the Modified Hoehn and Yahr Scale while in the OFF state, had been treated with levodopa for at least 1 year, had been on a stable Parkinson's disease regimen within normal therapeutic ranges including levodopa for at least 4 weeks before Baseline, were currently taking at least 3 doses of levodopa per day, had predictable end-of-dose wearing off, and had an average of at least 3 hours of OFF time per day on two valid 24-hour ON/OFF patient diaries prior to the Baseline visit.

Test Product, Dose and Mode of Administration, Batch Number:

Istradefylline 20 mg tablet, oral, batch number: C3K0015.

Istradefylline, 40 mg/day capsule, oral, batch numbers: 0256X; 0334X.

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Comparative Agents, Dose and Mode of Administration, Batch Number:
Placebo to istradefylline tablets, oral, batch number: C0281001.
Placebo to istradefylline capsules, oral, batch numbers: 0255X; 0315X; 0029A.
Entacapone, 200 mg tablets, oral, batch number: 1057484 and 1060568.
Entacapone, 200 mg capsules, oral, batch numbers: 0258X; 0261X; 0283X; 0346X; 0347X; 0371X; 0372X; 0376X.
Placebo to entacapone capsules, oral, batch numbers: 0236X; 0290X; 0322X; 0028A.

Duration of Treatment: A 2- to 3-week screening period followed by a 16-week double-blind treatment period.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable of this study was the change from Baseline in the percentage of awake time per day spent in the OFF state at Endpoint (Week 16 value or the last available post-Baseline value at the time of premature discontinuation from the study) based on data from the 24-hour ON/OFF patient diary (based on the home diary developed by RA Hauser et. al., 2000; hereafter to be referred to as the 24-hour ON/OFF patient diary).

The secondary efficacy endpoints included the actual values and changes from Baseline:

1. Based on the Subject's Valid 24-hour ON/OFF Patient Diary:

OFF State:

- Percentage and total hours of awake time per day spent in the OFF state at Weeks 2, 4, 6, 8, 12, and 16 (including actual values for percentage at Endpoint).

ON States Without Dyskinesia, With Dyskinesia, With Non-troublesome Dyskinesia, With Troublesome Dyskinesia, and Without Troublesome Dyskinesia (defined as the sum of the awake time per day spent in the ON state without dyskinesia plus the awake time per day spent in the ON state with non-troublesome dyskinesia):

- Percentage and total hours of awake time per day spent in the ON state at Weeks 2, 4, 6, 8, 12, 16, and Endpoint.

2. Based on UPDRS measured at Weeks 2, 4, 6, 8, 12, 16, and Endpoint
   - UPDRS Subscale I score (Mentation, Behavior, and Mood) in the ON state;
   - UPDRS Subscale II score (Activities of Daily Living) in the ON state and in the OFF state;
   - UPDRS Subscale III score (Motor Examination);
   - UPDRS Subscale I to III total score;
   - UPDRS Subscale II to III total score; and
   - UPDRS Subscale IVA score.
3. Based on Clinical Global Impression-Severity of Illness at Weeks 2, 4, 6, 8, 12, 16, and Endpoint.
4. Based on Parkinson's Disease Questionnaire
   - PDQ-39 total score and subscale scores at Weeks 4, 16, and Endpoint; and
   - PDQ-8 score at Weeks 4, 16, and Endpoint.
5. Based on Short Form-36 summary scores and subscales at Weeks 4, 16, and Endpoint.
6. Based on Patient Global Impression (actual values only) at Weeks 2, 4, 6, 8, 12, 16, and Endpoint.

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Criteria for Evaluation

Efficacy (continued):

In addition to the parameters described above, the change from Baseline in the percentage (and total hours) of awake time per day spent in the OFF state at Endpoint was summarized for the following subgroups: age group ($< 65, \geq 65$ years), gender, current smoker, food consumption within 30 minutes of study drug (Bottle A only) since previous visit, concomitant use of dopamine agonists, and concomitant use of either levodopa with carbidopa or levodopa with benserazide.

Safety:

The following measurements of safety were assessed during this study:

- Adverse events;
- Clinical laboratory test results (chemistry, hematology, and urinalysis);
- Vital signs;
- Weight;
- Physical and neurological examination findings; and
- 12-lead ECGs.

Pharmacokinetics:

For measurement of plasma KW-6002 concentrations (sparse sampling), blood was collected during the treatment period at Baseline and the Week 2, 4, 6, 8, 12, and 16 (or early discontinuation) visits. These data were used in the population pharmacokinetic/pharmacodynamic analysis and are the subject of a separate report.

Statistical Methods:

Demographic and Baseline Characteristics: A comparison among treatment groups for demographic and baseline characteristics was summarized descriptively. Continuous variables were summarized by providing the number of subjects, mean, standard deviation (SD), median, minimum, and maximum values; categorical variables were summarized by providing the number and percentage of subjects in each category.

Efficacy: All efficacy analyses were carried out based on the ITT analysis set.

The primary efficacy variable was analyzed using a main effects analysis of covariance (ANCOVA) model with terms for Investigator and treatment as factors and Baseline as a covariate. These terms were fitted as fixed effects and remained in the model regardless of their statistical significance. The test for treatment effects was carried out from this model.

A per-protocol (PP) analysis was performed as a secondary analysis for the primary efficacy variable. Any substantial differences between conclusions based on the ITT analysis set compared with the PP analysis set were investigated. Interpretation of p-values for the primary efficacy variable at assessment times other than Endpoint and all supportive and secondary efficacy variables at all assessment times were descriptive. In addition to the p-values, 95% confidence intervals for the differences in change from Baseline for continuous variables and in percentage of subjects for categorical variables were provided for the istradefylline and entacapone versus placebo treatment group differences. Additionally, for change from Baseline summaries, the 95% confidence intervals for the within treatment group change were provided.

All continuous supportive and secondary efficacy variables were analyzed using the main effects ANCOVA model. The CGI-S, change from Baseline for CGI-S (categorical summaries), and PGI-I variables were analyzed using a Cochran-Mantel-Haenszel (CMH) test using modified ridit scores and stratifying by Investigator.

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Statistical Methods (*continued*):

Safety:

Safety analyses were based upon data from the safety analysis set. All safety data collected in this study were summarized using descriptive statistics at each assessment time and Endpoint for the istradefylline, entacapone, and placebo groups based on actual values and change from Baseline values. No formal statistical comparisons of the istradefylline, entacapone, and placebo groups were made on the safety variables. All out-of-normal range results and clinically significant changes in any safety variable were identified in the subject data listings. Treatment-emergent adverse events were summarized by System Organ Class (SOC) and Preferred Term (using MedDRA 7.0) by number and percentage of subjects reporting an event and the number of events reported. Treatment-emergent adverse events were also summarized by maximum severity, closest relationship to study drug, seriousness, and those that resulted in death or led to withdrawal from the study. Descriptive statistics by group were provided for actual values and for change from Baseline values of vital signs, body weight, and laboratory results. Worst-case shift tables presenting changes from Baseline based on the normal ranges were also provided for the laboratory data. Physical examination findings and neurological examination findings were summarized with shift tables from Baseline to Endpoint. Descriptive statistics by group were provided for actual values and for change from Baseline in ECG results (ventricular heart rate, PR interval, QRS duration, QT and QTc interval). For overall interpretation of ECG results, a frequency distribution for the qualitative assessments was provided for all scheduled study visits. Shift tables from Baseline to worst value post-Baseline and listings of subjects with values meeting the potentially clinically significant (PCS) criteria for any safety variable are provided.

SUMMARY – CONCLUSIONS

Demographic and Baseline Characteristics: Of the 464 subjects in the safety analysis set, 284 (61.2%) were male and 314 (67.7%) were Caucasian. The mean age was 61.5 years. Four hundred and forty (94.8%) subjects were not smokers at Baseline. Demographic characteristics and Parkinson's disease history were similar among the 3 treatment groups. The mean percentage of awake time per day spent in the OFF state was 38.63% in the istradefylline group, 40.02% in the entacapone group, and 41.45% in the placebo group. The 3 treatment groups were also similar at Baseline for mean total hours of awake time per day spent in the OFF state: 6.17 hours in the istradefylline group, 6.47 hours in the entacapone group, and 6.60 hours in the placebo group. The 3 treatment groups were similar at Baseline for each of the secondary efficacy variables.

Efficacy Results:

The conclusions based on the efficacy analyses of the ITT analysis set (455 subjects) are as follows:

For the primary efficacy variable:

- *Change from Baseline to Endpoint in the Percentage Of Awake Time Per Day Spent in the OFF State*- LS mean reductions in the percentage of awake time per day spent in the OFF state from Baseline to Endpoint were 5.14% in the istradefylline group, 7.82% in the entacapone group, and 4.53% in the placebo group. Differences in LS mean reductions from Baseline to Endpoint in the percentage of awake time per day spent in the OFF state between the placebo and istradefylline groups and the placebo and entacapone groups were not statistically significant.

For the secondary OFF state efficacy variables:

- *Change from Baseline in Percentage of Awake Time Per Day Spent in the OFF State by Study Visit*-Reductions from Baseline to Weeks 2, 4, 6, 8, 12, and 16 were not statistically significant between the istradefylline and placebo groups. For the entacapone group, there were statistically significant differences from placebo; reductions were observed at Weeks 2, 4, 8, and 12 (p-values $\leq$ 0.05), but not at Weeks 6 and 16.

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Efficacy Results *(continued)*:

- *Total Hours of Awake Time Per Day Spent in the OFF State at Endpoint and by Study Visit* - The LS mean reductions in the total hours of awake time per day spent in the OFF state from Baseline to Endpoint were 0.77 hours in the istradefylline group, 1.22 hours in the entacapone group, and 0.70 hours in the placebo group; the LS mean differences from placebo were not statistically significant for either the istradefylline or the entacapone group. The LS mean differences from placebo were not statistically significant for the istradefylline group at any study visit. The LS mean reductions from Baseline to Weeks 2, 4, 8, and 12 were statistically significant (p-values $\leq$ 0.05) between the placebo and entacapone groups.

For the secondary ON state efficacy variables - change from Baseline at Endpoint:

- *ON State Without Dyskinesia* - There were no statistically significant differences versus placebo in LS mean increases in the percentage and total hours of awake time per day spent in the ON state without dyskinesia from Baseline at Endpoint for either the istradefylline or the entacapone group.
- *ON State With Dyskinesia* - There were no statistically significant differences in the istradefylline group versus the placebo group in LS mean increases in the percentage and total hours of awake time per day spent in the ON state with dyskinesia from Baseline at Endpoint. There were statistically significant (p-values $\leq$ 0.05) differences in the entacapone group versus the placebo group in LS mean increases in the percentage and total hours of awake time per day spent in the ON state with dyskinesia from Baseline at Endpoint of 4.02% and 0.71 hours.
- *ON State With Non-troublesome Dyskinesia* - There were no statistically significant differences versus placebo in LS mean increases in the percentage and total hours of awake time per day spent in the ON state with non-troublesome dyskinesia from Baseline at Endpoint for either the istradefylline or the entacapone group.
- *ON State With Troublesome Dyskinesia* - There was no statistically significant difference in the istradefylline group versus the placebo group in LS mean increases in the percentage or total hours of awake time per day spent in the ON state with troublesome dyskinesia from Baseline at Endpoint. There were statistically significant (p-values $\leq$ 0.05) differences in the entacapone group versus the placebo group in LS mean increases in the percentage and total hours of awake time per day spent in the ON state with troublesome dyskinesia from Baseline at Endpoint of 2.00% and 0.35 hours.
- *ON State Without Troublesome Dyskinesia* - There were no statistically significant differences versus placebo in LS mean increases in the percentage and total hours of awake time per day spent in the ON state without troublesome dyskinesia from Baseline at Endpoint for either the istradefylline or the entacapone group.

For the UPDRS efficacy variables - change from Baseline at Endpoint

- *UPDRS Subscales I and II (ON State)* - The LS mean differences in the reductions in each of the UPDRS Subscale I or Subscale II scores were not statistically significant for the istradefylline or the entacapone groups compared with the placebo group.
- *UPDRS Subscale II (OFF State)* - The LS mean difference in the reduction in UPDRS Subscale II score was not statistically significant for the istradefylline group compared with the placebo group. The LS mean difference in the reduction for the entacapone group compared with the placebo group was statistically significant (p = 0.016).
- *UPDRS Subscale III (ON State)* - The LS mean difference in the reduction in UPDRS Subscale III score was numerically better but not statistically significant (p = 0.064) at Endpoint for the istradefylline group compared with the placebo group. The LS mean difference in the reduction for the entacapone group compared with the placebo group was statistically significant (p = 0.043). The LS mean differences versus placebo showed numerical improvements in motor scores at Endpoint of -1.6 and -1.8, in the istradefylline and entacapone groups, respectively.

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Efficacy Results *(continued)*:

- *UPDRS Subscale I to III Total Score and UPDRS Subscale II to III Total Score* - The LS mean differences in the reductions in both of these total scores were not statistically significant for the istradefylline group compared with the placebo group. The LS mean differences in the reductions in both of these total scores were statistically significant (p-values $\leq$ 0.05) for the entacapone group compared with the placebo group.
- *UPDRS Subscale IVA Score (ON state)* - The LS mean differences in the reductions in UPDRS Subscale IVA scores were not statistically significant for either the istradefylline or the entacapone groups compared with the placebo group.

For the CGI-S, PDQ-39, PDQ-8, PGI-I, and SF-36, variables:

- *Clinical Global Impression-Severity of Illness (ON State) at Endpoint* - No statistically significant differences in the reductions in the CGI-S score were observed for either the istradefylline or the entacapone group, compared with the placebo group.
- *PDQ-39 Total Score (ON State) and PDQ-8 Total Score (ON State) at Endpoint* - There were no statistically significant differences in the reductions in the PDQ-39 or PDQ-8 total scores for either the istradefylline or the entacapone group, compared with the placebo group.
- *Patient Global Impression – Improvement at Endpoint* - The Overall Condition score for the istradefylline group versus placebo was not significantly different from that of the placebo group. There was a statistically significant difference at Endpoint for the entacapone group versus placebo (p = 0.044)
- *SF-36 at Endpoint*

  Physical Components Summary Score -There was no statistically significant difference in physical components summary score observed at Endpoint for the istradefylline group compared with the placebo group, while statistically significant improvements were observed at Endpoint for the entacapone group compared with the placebo group (p = 0.008).

  Mental Components Summary Score - There was no statistically significant difference in the mental components summary score observed from Baseline to Endpoint for either the istradefylline or the entacapone group compared with the placebo group.

Subgroup Analyses - For each specific subgroup considered (age group ($< 65, \geq 65$ years), gender, current smoker, food consumption within 30 minutes of study drug (Bottle A only) since previous visit, concomitant use of dopamine agonists, and concomitant use of either levodopa with carbidopa or levodopa with benserazide), there were no clinically meaningful differences in the 3 treatment groups in the percentage or total hours of awake time spent in the OFF state from Baseline to Endpoint.

Safety Results: The conclusions based on the safety analysis set (464 subjects) are as follows:
Study drug was well tolerated in all subjects who were randomized and received at least 1 dose of study drug. The percentage of subjects who completed the 16-week double-blind period were as follows: 92.5% of subjects in the istradefylline group, 85.0% of subjects in the entacapone group, and 87.5% of subjects in the placebo group

Adverse Events: The overall incidence of TEAEs was similar in all three groups: 103 (64.8%) subjects in the istradefylline group, 101 (66.0%) in the entacapone group, and 97 (63.8%) subjects in the placebo group.

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Safety Results *(continued)*:

Non-Serious Adverse Events

- The most frequently reported TEAEs in the istradefylline group were dyskinesia, tremor, and back pain. Dyskinesia was reported in 22 (13.8%) subjects in the istradefylline group, 20 (13.1%) subjects in the entacapone group, and 11 (7.2%) subjects in the placebo group. Tremor was reported for 10 (6.3%) subjects in the istradefylline group, 5 (3.3%) subjects in the entacapone group, and 7 (4.6%) subjects in the placebo group. Back pain was reported for 10 (6.3%) subjects in the istradefylline group, and in 4 (2.6%) subjects in each of the entacapone and placebo groups. Worsening Parkinson's disease was reported more frequently in the placebo group (11.2%) than in the istradefylline (5.7%) or the entacapone (7.2%) groups.
- The incidence of subjects with a TEAE that was considered by an Investigator to be related to study drug was 42.8% (68 subjects) in the istradefylline group, 46.4% (71 subjects) in the entacapone group, and 47.4% (72 subjects) in the placebo group.
- The most frequently reported TEAE considered possibly or probably related to study drug was dyskinesia reported by 21 (13.2%) subjects in the istradefylline group, 20 (13.1%) subjects in the entacapone group, and 11 (7.2%) subjects in the placebo group.
- The number of subjects with TEAEs that were considered to be severe was similar in each treatment. A total of 40 (8.6%) subjects experienced 90 severe TEAEs: 13 (8.2%) subjects with 26 events in the istradefylline group, 13 (8.5%) subjects with 33 events in the entacapone group, and 14 (9.2%) subjects with 31 events in the placebo group. The number of subjects with severe dyskinesia in the istradefylline and placebo groups was the same (i.e., 2 [1.3%] subjects in each group). In the entacapone group, 3 (2%) subjects experienced severe events of dyskinesia.

Deaths

- Three deaths were reported during the study: 1 death ("severe pneumonia" and "muscle rigidity" adverse events) in the placebo group and 2 deaths ("acute respiratory distress" and "heat stroke" adverse events, respectively) in the entacapone group. The death in the placebo group was considered by the Investigator to be related to study drug treatment and the 2 deaths in the entacapone group were considered unrelated to study drug treatment.

Other Serious Adverse Events

- A total of 16 subjects experienced 23 treatment-emergent serious adverse events: 5 (3.1%) subjects with 6 events in the istradefylline group, 5 (3.3%) subjects with 8 events in the entacapone group, and 6 (3.9%) subjects with 9 events in the placebo group.

Other Significant Adverse Events - Study Withdrawal

- The number of subjects who discontinued because of a TEAE was 7 (4.4%) subjects in the istradefylline group, 10 (6.5%) subjects in the entacapone group, and 10 (6.6%) subjects in the placebo group. Four subjects discontinued the study because of dyskinesia: 1 subject each in the istradefylline and placebo groups, and 2 subjects in the entacapone group. The 4 events of dyskinesia were mild to moderate in severity and none was considered serious.

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Safety Results *(continued)*:

Clinical Laboratory Evaluation, Vital Signs, Physical and Neurological Examination Findings, and ECG Findings:

- Approximately 20% of subjects had a PCS laboratory value; the incidence was similar in all groups with no relevant trends in the type of PCS laboratory value observed.
- No clinically significant differences were observed between the istradefylline and placebo groups for changes in clinical laboratory assessments, vital signs (sitting blood pressure and pulse rate), physical or neurological examinations, and ECGs.

Conclusions:

While no significant decrease in time in the OFF state for istradefylline group versus placebo was found, the findings of this study demonstrated that oral istradefylline at a daily dose of 40 mg in combination with levodopa and other dopamine agonists showed a numerical improvement in motor function as demonstrated by the Motor Subscale of the UPDRS and fewer reports of worsening of Parkinson's disease than placebo. Istradefylline was well tolerated in this patient population with a similar safety profile to placebo.

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