2 STUDY SYNOPSIS

<table>
<tr><td colspan="2">Name and Address of Sponsor/Company:
Kyowa Pharmaceutical, Inc.
212 Carnegie Center,
Suite 101
Princeton, NJ 08540

Kyowa Hakko UK Ltd.
258 Bath Road, Slough
Berkshire, UK SL1 4DX</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 colspan="2">Name of Finished Product:
Istradefylline</td></tr>
<tr><td colspan="2">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="4">Title of Study: A Long-Term, Multicenter, Open-Label Safety Study with Oral 20 or 40 mg/d Doses of KW-6002 (Istradefylline) as Treatment for Parkinson's Disease in Patients with Motor Response Complications on Levodopa Therapy (Protocol Number: 6002-INT-001)</td></tr>
<tr><td colspan="4">Investigator(s): 152 centers enrolled at least 1 subject</td></tr>
<tr><td colspan="4">Study Center(s): 97 centers in North America (United States and Canada) and 55 outside of North America (Austria, Argentina, Chile, Estonia, France, India, Italy, Latvia, Lithuania, Russia, South Africa, Spain, Ukraine, and the United Kingdom) enrolled subjects.</td></tr>
<tr><td colspan="4">Publication: None</td></tr>
<tr><td colspan="2">Studied Period: 08 October 2004 (Date of First Dose) to 01 March 2007 (Date of Last Dose)</td><td colspan="2">Clinical Phase: 3</td></tr>
<tr><td colspan="4">Objective: The primary objective of this study is to confirm the long-term tolerability and safety of oral 20 or 40 mg/day doses of istradefylline.</td></tr>
<tr><td colspan="4">Methodology: This is a long-term, multicenter, open-label study in which subjects with Parkinson's disease who had participated in a qualifying istradefylline trial were to be treated with istradefylline for a period of up to 1 additional year. Subjects were treated with istradefylline at a starting dosage of 40 mg/day and the maintenance dosage, either 20 mg/day or 40 mg/day, was based on tolerability and was at the discretion of the Investigator.</td></tr>
<tr><td colspan="4">Subject Population:
<u>Number of Subjects Enrolled</u>: 1242
<u>Number of Subjects Evaluated for Safety</u>: 1241</td></tr>
<tr><td colspan="4">Diagnosis and Main Criteria for Inclusion: Subjects with idiopathic Parkinson's disease who had previously participated in and completed (as defined by the specific protocol) participation in a qualifying istradefylline trial were eligible to participate in this long-term follow-on study. For sites in North America, subjects who discontinued prematurely from a qualifying double-blind trial were enrolled into the open-label trial only with approval by the Medical Monitor, accompanied by a signed waiver. Subjects who received istradefylline in long-term Study 6002-US-007 were enrolled at the discretion of the Investigator.</td></tr>
<tr><td colspan="4">Test Product, Dose and Mode of Administration, Batch number:
<u>Test Drug</u> — <u>Batch Number</u>
Istradefylline 20 mg tablets (oral administration) — C3K0015</td></tr>
<tr><td colspan="4">Comparative Agent, Dose and Mode of Administration, Batch Number: Not applicable.</td></tr>
<tr><td colspan="4">Duration of Treatment: 52 weeks</td></tr>
</table>

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Criteria for Evaluation:

Efficacy: The Modified Hoehn and Yahr Scale and Mini-Mental State Examination were administered at Screening and Week 52/Early Termination, but were not evaluated as efficacy endpoints.

Safety:

- Adverse events;
- Clinical laboratory tests (chemistry, hematology, and urinalysis);
- Vital signs and body weight;
- Physical and neurological examination findings; and
- 12-lead electrocardiogram.

Statistical Methods:

The safety analysis set was defined as all subjects who entered this study and took at least 1 dose of study drug during this open-label study.

Demographics and Baseline Characteristics: Demographic characteristics included age, race/ethnicity, and gender. Baseline characteristics included height, weight, body mass index, smoking status, Parkinson's disease history, Mini-Mental State Examination score, and Modified Hoehn and Yahr Scale score. The summaries included medical history for those subjects reporting any past or present conditions at Screening in this study. Demographic and Baseline characteristics were summarized descriptively for the safety analysis set. Continuous variables were summarized by number of subjects, mean, standard deviation, median, minimum, and maximum values. Categorical variables were summarized by number and percentage of subjects in each category. No statistical testing was performed.

Efficacy: Not applicable.

Safety: All safety data collected in this study were summarized using descriptive statistics at each assessment time and for Endpoint based on actual values and change from Baseline values. The Endpoint value for all subjects for each variable was the last available post-Baseline assessment. For subjects in Screening Group A (subjects with study drug interruption of $\leq$ 14 days), Baseline for all safety variables referred to the last available assessments obtained during the Screening period (which corresponded to the final visit of the previous istradefylline study). For subjects in Screening Group B (subjects with study drug interruption of > 14 days), Baseline for all safety variables referred to the Day -1 assessments, immediately prior to dispensing study drug in this study. If the Day -1 assessment was unavailable (e.g., either missing or not collected per protocol), then the Screening visit assessment at Week -2 was used as Baseline. Continuous variables were summarized using number of subjects, mean, standard deviation, median, minimum, and maximum values. Categorical variables were summarized using the number and percentage of subjects in each category. No formal statistical comparisons were made on the safety variables. All out-of-normal-range results and potentially clinically significant (PCS) changes in any safety variable were flagged in the subject data listings.

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SUMMARY OF RESULTS

Demographics and Baseline Characteristics Results:

The safety analysis set included 1241 subjects: mean age was 63.1 years and 66.0% were male. The majority (86.6%) were Caucasian, 8.3% were Asian, 2.7% were Hispanic, and the remainder were Black (0.9%), American Indian (0.1%), or reported as "other" race/ethnicity (1.4%). Overall, 3.7% of subjects were current smokers. For Parkinson's disease history, the mean time since diagnosis was 9.43 years, initiation of levodopa was 8.12 years, and onset of motor complications was 4.02 years. The mean score for the Mini-Mental State Examination was 29.0 and the Modified Hoehn and Yahr Scale was 2.61.

Efficacy Results:

Not applicable.

Safety Results:

The safety analysis set for this open-label study comprised 1241 subjects who had participated in prior clinical trials of istradefylline. Subjects who had previously participated in the open-label Study 6002-US-007 had an interruption in dosing with istradefylline of at least 1 year. For subjects in the safety analysis set, the mean duration of therapy was 43.82 weeks.

Adverse Events:

Overall, 88.6% of subjects experienced TEAEs. The incidences of common TEAEs that are considered to be medically important are as follows: dyskinesia (32.3%), insomnia (11.0%), hallucination (8.0%), depression (7.7%), lightheadedness (6.7%), peripheral edema (6.4%), freezing phenomenon (5.3%), and balance disorder (5.0%).

For 68.3% of subjects, TEAEs were assessed by Investigators as related to study drug. The most common drug-related TEAEs were dyskinesia (29.9%), worsening of Parkinson's disease (12.1%), constipation (7.0%), hallucination (6.9%), and insomnia (6.7%).

Most subjects experienced TEAEs that were reported as mild or moderate in severity. Severe TEAEs were reported for 21.3% of subjects (264 subjects). The most common severe TEAEs were dyskinesia (2.7% [33 subjects]) and worsening of Parkinson's disease (2.3% [28 subjects]). For 2.3% of subjects (29 subjects), TEAEs of dyskinesia were considered by the Investigators to be both severe and related to study drug. For subjects with severe dyskinesia, study drug was withdrawn for 7 subjects and the dosage was reduced for 6 subjects because of the dyskinesia.

Deaths that resulted from treatment-emergent serious adverse events (SAEs) were reported for 7 subjects in this study. One of the deaths (reported as sudden death) was considered by the Investigator and the Sponsor to be possibly related to study drug. For another subject, a fatal SAE of cardio-respiratory arrest occurred more than 30 days after the last dose of study drug.

During this study, treatment-emergent SAEs were reported for 15.1% of subjects (187 subjects) and were assessed by Investigators as drug-related for 3.9% of subjects (49 subjects).

Treatment-emergent adverse events that led to study discontinuation were reported for 11.5% of subjects (143 subjects) and were assessed as drug-related for 8.4% of subjects (104 subjects). Forty-nine subjects withdrew from the study because of SAEs.

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Clinical Laboratory Evaluations, Vital Signs, Physical Examination and Neurological Findings, and Electrocardiograms:

A total of 576 subjects (46.4%) had treatment-emergent laboratory values that met the PCS criteria. The most frequently observed hematology parameters that met the PCS criteria (> 2.0% of subjects) were hemoglobin (69 subjects), white blood cell count (46 subjects), hematocrit (43 subjects), and red blood cell count (32 subjects). The most frequently observed (> 2.0% of subjects) PCS chemistry values were blood urea nitrogen (151 subjects), potassium (35 subjects), uric acid (31 subjects), sodium (29 subjects), and glucose (28 subjects).

The change in mean body weight from Baseline to Endpoint was -1.10 kg. A total of 245 subjects (19.7%) experienced PCS changes in body weight: 5.5% had PCS increases and 14.4% had PCS decreases, including 2 subjects who had both increases and decreases in weight during the study that met the PCS criteria. Thirty-six subjects (2.9%) experienced TEAEs of decreased weight and 6 subjects (0.5%) experienced TEAEs of increased weight that were considered to be related to the study drug.

No clinically important overall trends in clinical laboratory assessments, vital signs (sitting blood pressure and pulse rate), physical examinations, electrocardiograms, or neurological examinations were observed.

CONCLUSIONS: During Study 6002-INT-001, istradefylline was well tolerated as adjunctive therapy to levodopa for subjects with Parkinson's disease. More than 70% of the subjects in this study completed the 52-week treatment period. In addition, the average overall dose of istradefylline that was taken by study participants (37.12 mg/day) approached 40 mg/day, which was the highest allowed dose in this study.

Date of report: 14 August 2007