CLINICAL PROTOCOL

Protocol Title:	A Phase 3, Long-term, Open-label Study of Istradefylline in Subjects with Moderate to Severe Parkinson's Disease
Protocol Number:	6002-018
Original Protocol:	28SEP2015
Test Drug:	Istradefylline
Phase:	Phase 3
Study Design:	Open-label, flexible-dose, multicenter study to evaluate the safety of istradefylline
Indication:	Moderate to severe Parkinson's disease
US IND Number:	58,356
EudraCT Number:	2015-003887-34
Sponsor:	Kyowa Hakko Kirin Pharma, Inc. 212 Carnegie Center, Suite 101 Princeton, NJ 08540
Sponsor's Responsible Medical Monitor:	Yao Wang MD, MS Director, Medical Research 609-580-7441

Principal Investigator Signature Page

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Protocol Number: 6002-018

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Any supplemental information (e.g., protocol amendment, Investigator's Brochure, study manuals) that may accompany this document is also proprietary to KKP and should be handled consistent with the terms stated above.

I, the undersigned, have reviewed this protocol, including Appendices and I agree to conduct the clinical study in compliance with the protocol and study manuals, and with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC. I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the Sponsor, involves only logistical or administrative changes.

Principal Investigator:

Signature	Date
Printed Name	Title
Institution Address	Telephone Number

Protocol Signature Page

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29SEP2015

Stephen Letrent, PharmD, PhD, BCPS
Senior Vice President, Drug Development
Kyowa Hakko Kirin Pharma, Inc.
212 Carnegie Center, Suite 101
Princeton, NJ 08540

Date

1 CLINICAL STUDY PROTOCOL SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Kyowa Hakko Kirin Pharma, Inc.
212 Carnegie Center, Suite 101
Princeton, NJ 08540</td><td rowspan="3">Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:

Volume:

Reference:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Istradefylline film-coated tablets</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 Phase 3, Long-term, Open-label Study of Istradefylline in Subjects with Moderate to Severe Parkinson's Disease</td></tr>
<tr><td colspan="3">Protocol Number: 6002-018</td></tr>
<tr><td colspan="3">Investigators and Study Centers: Approximately 90 clinical sites in the United States (US), European Union (EU), and the rest of the world will participate in the study.</td></tr>
<tr><td colspan="3">Phase of Development: Phase 3</td></tr>
<tr><td colspan="3">Primary Objective: To evaluate the long-term safety and tolerability of oral istradefylline 20 to 40 mg/d as treatment for subjects with moderate to severe Parkinson's Disease (PD).</td></tr>
<tr><td colspan="3">Methodology/Study Design:

This is a Phase 3, 52-week, open-label, flexible-dose, multinational, multicenter study to evaluate the safety and tolerability of istradefylline 20 to 40 mg/d in subjects with moderate to severe PD with motor fluctuations and dyskinesia on levodopa combination (levodopa/carbidopa or levodopa/benserazide) therapy plus at least one adjunctive PD medication.

Subjects who completed 12 weeks of double-blind treatment and the 30-day follow-up period in Study No. 6002-014 will undergo Screening and Baseline evaluations for eligibility for the study. Eligible subjects will initially be treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at Week 12 based on the Investigator's judgment of each subject's response and tolerability. If deemed necessary, one unscheduled dose adjustment visit between Week 2 to Week 12 is allowed in accordance with clinical judgment of the Investigator. Subjects who had a dose adjustment to 40 mg/d can have their dose decreased to 20 mg/d by the Investigator at a second unscheduled dose adjustment visit if there are tolerability issues. The istradefylline dose should remain fixed between Week 26 to Week 52. Consultation with the Sponsor's Medical Monitor is required prior to any unscheduled dose adjustment visits. A subject may discontinue from the study at any time.

Safety Outcomes (Primary): Adverse events (AEs) and clinical laboratory tests (hematology, chemistry, and urinalysis).

Efficacy Outcomes (Secondary): The change from Baseline in the score of the Patient Global Impression-Improvement (PGI-I) Scale at Week 12, Week 26, and Week 52.</td></tr>
<tr><td colspan="3">Diagnosis/Selection of Subjects: Subjects with PD with motor fluctuations and dyskinesia on levodopa combination (levodopa/carbidopa or levodopa/benserazide) therapy plus at least one adjunctive PD medication who completed Study No. 6002-014.</td></tr>
<tr><td colspan="3">Number of Subjects/Centers Planned: Approximately 300 subjects at up to 90 centers.</td></tr>
</table>

Name of Sponsor/Company: Kyowa Hakko Kirin Pharma, Inc. 212 Carnegie Center, Suite 101 Princeton, NJ 08540	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:**	**(For National Authority Use Only)**
Name of Finished Product: Istradefylline film-coated tablets	**Volume:**	
Name of Active Ingredient: (*E*)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione	**Reference:**	

Criteria for Inclusion:

- Subjects who have given written informed consent;
- Subjects who completed 12 weeks of double-blind treatment and the 30-day follow-up period in Study No. 6002-014;
- Subjects who are currently taking levodopa combination (carbidopa/levodopa or benserazide/levodopa) therapy plus at least one adjunctive PD medication;
- Women of child-bearing potential (WOCBP) must use a reliable method of contraception (e.g., oral contraceptive or long-term injectable or implantable hormonal contraceptive, double barrier methods [such as condom plus diaphragm, condom plus spermicide foam, condom plus sponge], or intra-uterine devices), and must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline.
  - WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization or is not post-menopausal (defined as amenorrhea $\geq$ 24 consecutive months or a serum follicle-stimulating hormone [FSH] $\geq$ 30 IU/L in the absence of hormone replacement therapy.

Criteria for Exclusion:

- Subjects whose treatment compliance was less than 70% throughout their enrollment in Study No. 6002-014;
- Subjects who are currently treated with apomorphine and/or dopamine receptor antagonists (paliperidone, clozapine, risperidone, olanzapine, quetiapine [except for 100 mg/d or less for levodopa- or PD-induced hallucinations], ziprasidone, aripiprazole, asenapine, and lurasidone, etc.) or direct gastrointestinal levodopa infusion;
- Subjects who have been treated within 30 days before Baseline (or five half-lives of the compound, if longer) with any investigational agents other than istradefylline;
- Subjects who have undergone a neurosurgical procedure for PD (e.g., pallidotomy, thalamotomy, or deep brain stimulation);
- Subjects who are currently receiving another A_{2A} antagonist (except for caffeine which is allowed);
- Subjects who are taking potent CYP3A4 inhibitors (systemic antifungals such as ketoconazole);
- Subjects who are taking potent CYP3A4 inducers (such as St John's Wort and rifampin);
- Subjects who have had a diagnosis of cancer or evidence of continued malignancy within the past three years (with the exception of adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or in situ prostate cancer with a normal prostate-specific antigen post resection);
- Subjects with major protocol deviations in Study No. 6002-014 (subjects who failed to meet any of the inclusion criteria, subjects who met any of the exclusion criteria or subjects who met the criteria for subject withdrawal but who were not withdrawn);
- Subjects who, for any reason, are judged by the Investigator to be inappropriate for this study, including a subject who is unable to communicate or to cooperate with the Investigator or who has/had a clinically significant illness or abnormal physical examination that may compromise the safety of the subject during

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the study or affect the ability of the subject to adhere to study procedures;

- Subjects who have clinical laboratory test results that are clinically unacceptable by the Investigator, or who have an alanine aminotransferase and/or an aspartate aminotransferase level > 3 times the upper limit of normal (ULN), and serum total bilirubin > 2 times the ULN at Screening;
- Subjects who have untreated major depressive disorder;
- Subjects who have a history of seizures or seizure disorders;
- Subjects who have a history of neuroleptic malignant syndrome;
- Subjects with suicidal behavior within the previous month;
- Subjects who have a history of drug or alcohol abuse or dependence within the last year by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision;
- Subjects who are pregnant (confirmed by beta human chorionic gonadotropin [β-HCG]), plan to become pregnant, or are breastfeeding.

Test Products:

- **Study Drug**: Istradefylline tablets, 20 mg/d or 40 mg/d, oral administration
- **Duration of Treatment**: 7-day Screening period, 52 weeks of open-label treatment, followed by 30 days of safety follow-up period.

Efficacy and Safety Variables

Efficacy (Secondary):

- PGI-I Scale: change in score from Baseline at Weeks 12, 26, and 52 visits

Safety (Primary):

- Adverse events (AEs);
- Clinical laboratory tests (chemistry, hematology, and urinalysis), and serum / urine pregnancy tests.

Statistical Analysis: The overall incidence of treatment-emergent adverse events (TEAEs) will be summarized by System Organ Class (SOC) and by Preferred Term (PT) using the number and percentage of subjects reporting an event and by the number of events reported. TEAEs will also be summarized by maximum severity (mild, moderate, or severe) and closest relationship (related or not related). Serious TEAEs, TEAEs leading to study discontinuation, and TEAEs with an outcome of death will be presented in separate listings. Descriptive statistics will be provided for actual values and change from Baseline clinical laboratory tests (serum chemistry, hematology, and urinalysis) at each assessment time for the safety analysis set. Vital signs and physical examination findings will be summarized using actual values at Screening. Screening electrocardiogram (ECG) interpretations will be listed. Clinical laboratory tests categorized as in or out of normal range will be summarized using worst-case shift tables.

All out-of-normal-range results in any safety variable will be flagged in the subject data listings.

Actual values and change from Baseline PGI-I values will be summarized at each time point collected using descriptive statistics.

2 TABLE OF CONTENTS

List of In-text Tables

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

A_{2A}	adenosine A_{2A} receptor
AE	adverse event
β-HCG	beta human chorionic gonadotropin
BP	blood pressure
COMT	catechol-O-methyltransferase
CNS	central nervous system
CTA	clinical trial agreement
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
EU	European Union
FDA	Food & Drug Administration
FSH	follicle-stimulating hormone
GABA/ENK-MSN	γ-amino butyric acid and enkephalin-containing medium spiny neurons
GCP	Good Clinical Practice
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	International Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat Set
KKP	Kyowa Hakko Kirin Pharma, Inc
LS	Least squares
MAO-B	monoamine oxidase B
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride
PD	Parkinson's disease
PGI-I	Patient Global Impression - Improvement Scale
P-gp	P-glycoprotein
PK	pharmacokinetic
PT	Preferred Term
SAE	serious adverse event
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WOCBP	women of child-bearing potential

Definitions

AUC	area under the concentration-time curve
C_{max}	observed maximum plasma concentration
QT interval	in electrocardiography, the time from the beginning of the QRS complex to the end of the T wave (interval)
$t_{1/2}$	terminal half-life
t_{max}	time to maximum plasma concentration

4 INTRODUCTION

4.1 Medical Background

Parkinson's disease (PD), one of the most common neurodegenerative disorders, is characterized by the loss of dopamine-generating neurons projecting from the substantia nigra to striatum nuclei causing bradykinesia or akinesia, rigidity, and resting tremor. The most effective therapies for PD are drugs that enhance dopaminergic neurotransmission in the brain, most commonly, levodopa. Chronic therapy with levodopa is associated with declining efficacy and the development of motor complications such as end-of-dose deterioration or wearing-off, peak-dose dyskinesias, and ON-OFF phenomenon. Adjunctive therapies such as catechol-O-methyltransferase (COMT) inhibitors may be added to a patient's treatment regimen to reduce peripheral conversion of levodopa and extend this drug's benefit or monoamine oxidase B (MAO-B) inhibitor can be used to extend the dopaminergic effect of levodopa in the brain. However, both have side effects including nausea, orthostatic hypotension, hallucinations, or compulsive behaviors. At the most advanced stage of the illness, intestinal infusion of Duodopa® (levodopa plus carbidopa in a microsuspension) or surgical techniques such as deep brain stimulation may be required to provide adequate symptom control. Therefore, an unmet clinical need exists for the development of novel approaches to augment the actions of established therapies in individuals with advanced PD.

The adenosine A_{2A} receptor (A_{2A}) receptors in the striatum are located predominantly on the γ-amino butyric acid and enkephalin-containing medium spiny neurons (GABA/ENK-MSN) that form the indirect output pathway from the striatum to the globus pallidus. Loss of dopaminergic neurons in the substantia nigra compacta reduces the normal inhibition of the nigrostriatal pathway on the GABA/ENK-MSN, resulting in an increase in the excitability of the indirect pathway. Activation of A_{2A} receptors increases the excitability of the striatopallidal pathway via adenosine A_{2A} receptors expressed on medium spiny neurons. Therefore, blockade of the receptors in the striatum and globus pallidus results in a decrease in the excessive activation in the indirect pathway, and provides an alternative, non-dopaminergic approach to the symptomatic relief of PD.

4.2 Study Drug Profile

Istradefylline is a highly selective adenosine A_{2A} antagonist currently under development as a treatment for the signs and symptoms of PD. Among four adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3) within the human central nervous system (CNS), the adenosine A_{2A} receptor is located almost exclusively in the basal ganglia. There is evidence that A_{2A} receptors located on the striatopallidal medium spiny neurons, in the indirect pathway, are involved in motor control via the basal ganglia. It is hypothesized that blockage of the A_{2A} receptors by istradefylline reduces the excitability of this indirect pathway of the basal ganglia, resulting in an improvement in PD symptoms. Adenosine A_{2A} receptor antagonists were found to be active in several behavioral pharmacology studies in animal models for PD and depression. Istradefylline has shown no significant affinity for other neurotransmitter receptors including dopamine, acetylcholine, serotonin, and norepinephrine.

Istradefylline was approved in Japan on 25MAR2013 under the trade name NOURIAST® tablets, and was marketed on 30MAY2013.

4.2.1 Data from Non-clinical Studies

Istradefylline was found to be active in a number of rodent and non-human primate models of PD. Istradefylline improved catalepsy and locomotor depression, and enhanced rotational behavior in various experimental rodent models, and its activity was manifested through an interaction with the adenosine A_{2A} receptor. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP)-treated marmoset and cynomolgus monkeys, istradefylline given as monotherapy ameliorated motor disability without inducing dyskinesia. When given with levodopa in MPTP-treated marmoset monkeys, istradefylline potentiated and prolonged the effects of single doses of levodopa.

In animal safety pharmacology studies of istradefylline, increased blood pressure, and heart rate observed at relatively low doses in rats were not dose-dependent in duration or in magnitude. These changes were considered to be due to the increased locomotor activity observed. In conscious dogs, istradefylline had no clinically significant effect on the cardiovascular system, the respiratory system, general activity and behavior, or body at doses of 160 mg/kg up to 400 mg/kg. Istradefylline did not inhibit the human ether-a-go-go-related gene tail current in vitro. In telemetered dogs, istradefylline at a dose of 1000 mg/kg administered daily by gavage for six weeks did not affect the QT interval corrected for heart

rate or respiration rate. Istradefylline produced small but significant, dose-related increases in body temperature in mice, rats, and rabbits.

4.2.2 Data from Clinical Studies

To date, a total of 49 clinical studies have been completed as part of the clinical development program for istradefylline. These consist of 27 Phase 1 studies, and 22 Phase 2 to 3 studies including approximately 3750 subjects who received istradefylline. Istradefylline has been administered to approximately 2830 subjects with PD (combination therapy and monotherapy), 222 subjects with Major Depressive Disorder, and 104 subjects with Restless Legs Syndrome.

Istradefylline has been administered in single doses of up to 400 mg in healthy volunteers. In controlled, Phase 2 and 3 studies in subjects with PD, doses of 10 to 60 mg/d were administered for 12-16 weeks to approximately 2000 subjects. In addition, istradefylline has been administered at doses of 20 to 60 mg/d in four Phase 3 long-term follow-on safety studies in which approximately 2550 PD subjects have been exposed to istradefylline for periods up to two years. The mean exposure for subjects treated in the combined long-term open-label istradefylline studies was 46.4 weeks.

In addition, there is one ongoing Phase 3, double-blind, multicenter, placebo-controlled study of istradefylline 20 or 40 mg/d for 12 weeks in Parkinson's disease that is currently enrolling subjects (Study No. 6002-014). As of 26AUG2015, 437 subjects were enrolled in the study.

4.2.2.1 Pharmacokinetics and Pharmacodynamics

The istradefylline pharmacokinetics (PK) have been characterized in healthy subjects, renally impaired and hepatically impaired subjects in a number of Phase 1 studies. Istradefylline has a moderate rate of absorption (Time to maximum plasma concentration [t_{max}] 2-5 hours) and slow elimination (average half-life across Phase 1 studies: 70-148 hours). Increases in systemic exposure are dose-proportional up to 80 mg/d, and slightly less than proportional at 160 mg/d. Pharmacokinetics are time independent following multiple doses compared to single doses.

Istradefylline is metabolized through oxidative pathways (Phase I metabolites by major metabolic isozymes: cytochrome P450 [CYP] 1A1, CYP3A4, and CYP3A5; by minor isozymes: CYP1A2, CYP2B6, CYP2C8, CYP2C18, and CYP2D6*1), followed by

conjugation (Phase II pathways) to sulfate or glucuronic acid. The major circulating species in plasma and feces is the parent compound, and each Phase I and Phase II metabolite comprises less than 10% of the area under the concentration time curve (AUC) of the parent compound. Istradefylline demonstrated moderate CYP3A4 inhibition only at supra-therapeutic doses. Increased systemic exposure may occur following co-administration of istradefylline with potent CYP3A4 inhibitors, such as ketoconazole. Rifampin, a strong CYP3A4 enzyme inducer, decreased the maximum plasma concentration (C_{max}) and AUC of istradefylline by 44.5% and 80.8%, respectively. Istradefylline is a mild inhibitor of P-glycoprotein (P-gp), after co-administration with digoxin, 33% increases in digoxin C_{max} and 20% increases in AUC were observed.

Co-administration of istradefylline with a high-fat meal leads to 25% increase in AUC and 64% increase in C_{max}; however, increased systemic exposure is not associated with decreased tolerability when administered with a meal and istradefylline can be administered under fed or fasted conditions. There is no relevant effect of severe renal impairment, age, sex, race, and disease state (PD) on systemic exposure to istradefylline. Smokers (1 pack/day) have 36%-42% lower systemic exposure compared to non-smokers.

A positron emission topography study with istradefylline demonstrated greater than 90% adenosine A_{2A} receptor occupancy at doses greater than 5 mg/d. In addition, population PK/pharmacodynamic analysis of clinical studies indicated incremental improvement in efficacy at doses of 20 mg/d and 40 mg/d, but little clinically meaningful additional improvement at 60 mg/d. A plateau in the incidence of dizziness and dyskinesia as adverse events (AEs) was observed at doses of 40 mg, and an increase in the incidence of nausea was observed at doses beyond 40 mg/d.

4.2.2.2 Efficacy

Treatment with istradefylline resulted in clinically meaningful and statistically significant ($p \leq 0.05$) differences from placebo in the reductions from Baseline to Endpoint in the percentage of awake time per day spent in the OFF state for subjects receiving levodopa as well as other antiparkinson's medications in three Phase 2b/3 studies (Study No. 6002-US-005, LeWitt, 2008; Study No. 6002-US-006, Stacy, 2008; and Study No. 6002-US-013, Hauser, 2008).

In Study No. 6002-US-005 (LeWitt, 2008), the mean percentage of awake time per day spent in the OFF state at Baseline was 38.44% for the 40 mg/d istradefylline group and 37.19% for

the placebo group. The least squares (LS) mean change from Baseline to Endpoint in the percentage of awake time per day spent in the OFF state was -10.49% for the 40 mg/d istradefylline group and -3.71% for the placebo group.

In Study No. 6002-US-006 (Stacy, 2008), the mean percentage of awake time per day spent in the OFF state at Baseline showed were 34.81% and 35.07% for the 20 and 60 mg/d istradefylline groups, respectively, and 36.56% for the placebo group. The LS mean changes from Baseline to Endpoint in the percentage of awake time per day spent in the OFF state were -7.72% and -7.84% in the 20 and 60 mg/d istradefylline groups, respectively, and -4.07% in the placebo group.

In Study No. 6002-US-013 (Hauser, 2008), the mean percentage of awake time per day spent in the OFF state at Baseline were 39.81% in the 20 mg/d istradefylline group and 38.72% in the placebo group. The LS mean change from Baseline to Endpoint in the percentage of awake time per day spent in the OFF state was -9.49% in the 20 mg/d istradefylline group and -4.92% for the placebo group.

Information regarding the efficacy results from all studies conducted with istradefylline is available in the Investigator's Brochure.

4.2.2.3 Safety

As noted above, istradefylline has been administered at doses of 20 to 60 mg/d in four Phase 3 long-term follow-on safety studies in which approximately 2550 PD subjects have been exposed to istradefylline for periods up to two years.

A Phase 3 open-label study evaluated the long-term safety and tolerability (Study No. 6002-US-007) of istradefylline of 20, 40, or 60 mg/d in PD subjects for up to 52 weeks who had participated in a previous study. Istradefylline was well tolerated for a mean treatment duration of 25.4 weeks with over 52 weeks treatment for some subjects. The most frequently reported AEs were dyskinesia, dizziness, and nausea.

A Phase 3 open-label international study evaluated the long-term safety and tolerability (Study No. 6002-INT-001) of istradefylline of 20 or 40 mg/d for up to 52 weeks in PD subjects who had participated in a previous study. Istradefylline was well tolerated. The most frequently reported treatment-related AEs included dyskinesia, worsening of Parkinson's disease, constipation, hallucination, and insomnia.

A Phase 3 open-label study (Study No. 6002-US-025) of istradefylline of 20 or 40 mg/d for up to two years was conducted in PD subjects who completed Study No. 6002-INT-001. Istradefylline was well-tolerated in subjects. The most frequently reported AEs were worsening of Parkinson's disease, dyskinesia, accident, and hallucination.

A Phase 3 open-label study conducted in Japan (Study No. 6002-010, Kondo, 2015) in PD patients showed that the efficacy of long-term istradefylline 20 or 40 mg/d persisted for 52 weeks and that the safety profile was not substantially different between the subjects who had been exposed to istradefylline and those who were newly exposed to istradefylline in the open-label phase. In addition, treatment with long-term istradefylline was not associated with delayed events raising safety concerns.

Results from clinical studies conducted to date suggested that istradefylline is well tolerated. These data also indicate that istradefylline can be taken with the patient's existing PD medications without an increase in safety concerns. There have been no studies with istradefylline in pregnant women. Treatment with this study drug may involve unforeseeable risks to the mother or the unborn baby if exposed before birth. For this reason, any female who is pregnant or trying to become pregnant will be excluded from research studies. Because the drug passes into breast milk, females who are breastfeeding will not be allowed to participate in research studies.

Information regarding the safety results from all studies conducted with istradefylline is available in the Investigator's Brochure.

5 RATIONALE FOR CONDUCTING THE STUDY, OBJECTIVES, AND RISK/BENEFIT ASSESSMENT

5.1 Rationale for Performing the Study

The purpose of this study is to evaluate the long-term safety and tolerability of istradefylline (20 to 40 mg/d) in subjects with moderate to severe PD with motor fluctuations and dyskinesia on levodopa combination (levodopa/carbidopa or levodopa/benserazide) therapy plus at least one adjunctive PD medication in an open-label setting for up to 52 weeks of treatment.

5.2 Study Objectives

The study objective and the outcome measures of the study are shown in Table 5.2-1.

Table 5.2-1 Study Objective/Outcome Measures/Endpoints

Objective	Outcome Measures/Endpoints
Primary Objective: To evaluate the long-term safety and tolerability of oral istradefylline (20 to 40 mg/d) as treatment for subjects with moderate to severe PD.	**Safety endpoints (Primary):** The safety endpoints are the following: • AEs and SAEs • Clinical laboratory assessments **Efficacy endpoint (Secondary):** • PGI-I Scale: Change in score from Baseline at Weeks 12, 26, and 52

AE=adverse event; PD=Parkinson's disease; PGI-I=Patient Global Assessment Impression - Improvement Scale; SAE=serious adverse event

See Section 10 for details of variables assessed.

5.3 Risk/Benefit Assessment

5.3.1 Risks

Safety and tolerability data from clinical studies conducted in over 3700 subjects suggest that istradefylline is well tolerated. Only dyskinesia and nausea were reported in > 5% incidence in clinical study populations.

Istradefylline should not be administered to subjects who are taking potent CYP3A4 inhibitors or inducers. Istradefylline is also a mild inhibitor of P-gp. It should also not be administered to subjects who are pregnant or breastfeeding.

For complete safety information, refer to the Investigator's Brochure.

5.3.2 Benefits

Clinical studies conducted in subjects with moderate to severe PD have shown that istradefylline offers an improvement in OFF time starting at Week 2 of treatment and was well-tolerated. Being a non-dopaminergic treatment, it seems to cause no increase in troublesome dyskinesia over standard of care combination therapy (non-troublesome dyskinesia may increase), and has a manageable side-effect profile.

Given the above considerations, the risk benefit assessment is considered favorable for the initiation and conduct of this study.

6 DESCRIPTION OF SUDY DESIGN AND POPULATION

6.1 Overall Study Design and Plan

This is a Phase 3, 52-week, open-label, flexible-dose, multinational, multicenter study to evaluate the safety and tolerability of istradefylline 20 or 40 mg/d in subjects with moderate to severe PD with motor fluctuations and dyskinesia on levodopa combination (levodopa/carbidopa or levodopa/benserazide) therapy plus at least one adjunctive PD medication.

Subjects who completed 12 weeks of double-blind treatment and the 30-day follow-up period in Study No. 6002-014 will undergo Screening and Baseline evaluations for eligibility for the study. Eligible subjects will be treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at Week 12 based on the Investigator's judgment of each subject's response and tolerability. If deemed necessary, one unscheduled dose adjustment visit between Week 2 to Week 12 is allowed in accordance with clinical judgment of the Investigator. Subjects who had a dose adjustment to 40 mg/d can have their dose decreased to 20 mg/d by the Investigator at a second unscheduled dose adjustment visit if there are tolerability issues. The istradefylline dose should remain fixed between Week 26 to Week 52. Consultation with the Sponsor's Medical Monitor is required prior to any unscheduled dose adjustment visits. A subject may discontinue from the study at any time.

6.1.1 Main Diagnosis for Study Entry

Subjects with moderate to severe PD who completed Study No. 6002-014 are eligible to participate in this roll-over study.

6.1.2 Administrative Structure of the Study

The overall management and organization of this study will be overseen by Kyowa Hakko Kirin Pharma Inc. (KKP) (hereinafter referred to as the Sponsor). The Principal Investigators will review and sign the Clinical Trial Agreement (CTA). A central laboratory will be utilized. All study-related documents will be stored in the Clinical Trial Master File and each

individual site. Contact information for reporting serious adverse events (SAEs) is shown in Table 6.1.2-1.

Table 6.1.2-1 Serious Adverse Event Contacts

Serious Adverse Event FAX : +1-800-209-2251 **Email: saesource@kyowa-kirin-pharma.com**
Medical Monitor Yao Wang, MD, MS Kyowa Hakko Kirin Pharma, Inc. 212 Carnegie Center, Suite 101 Princeton, NJ 08540 Phone: +1-609-580-7441 Fax: +1-609-919-1111 **24 HR Contact: +1-973-873-8678**
Sr. Clinical Trial Manager Georgina Spence Prostrakan Galashiels, Scotland Phone: +44 (0)1896 668 170 georgina.spence@prostrakan-khk.com
Drug Safety Surveillance Kyowa Hakko Kirin Pharma, Inc. 212 Carnegie Center, Suite 101 Princeton, NJ 08540 Phone: +1-609-919-1100 Fax: +1-609-919-1111

6.2 Discussion of Study Design

This open-label study is designed to evaluate the long-term safety and tolerability of flexible doses of istradefylline for 52 weeks in PD. The flexible-dose design was selected to examine the relative safety and tolerability of istradefylline at a range of dosages based on the Investigator's judgment (i.e., in a manner applicable to the expected clinical use). The 30-day

safety follow-up period allows continued subject monitoring after the study drug has been discontinued.

6.3 Selection of Doses in the Study

The daily doses of study drug, istradefylline 20 mg/d or 40 mg/d were chosen since they were the doses the subjects received in Study No. 6002-014. Study drug will be taken in the morning for the duration of study participation on an outpatient basis. Study drug may be taken with or without food.

6.4 Study Timeframe and Duration

Subjects will participate in the study for up to a total of 57 weeks from Screening through Follow-up. This open-label study is comprised of a 7-day Screening period (subjects must have completed 12 weeks of double-blind treatment and the 30-day follow-up period in Study 6002-014), followed by Baseline, and visits at Week 12, Week 26, and Week 52. Each subject will also be followed for 30 days after discontinuation from the study for safety. Subjects may remain in the study for 52 weeks or until any of the other criteria for study removal are met.

6.5 Number of Subjects, and Numbers and Location of Investigative Sites

Approximately 300 subjects who completed Study No. 6002-014 are estimated to be enrolled in the study. This is a global clinical study. Approximately 90 clinical sites will participate from the United State (US), Europe (EU), and the rest of the world.

6.6 Definition of End of Study

The end of study is the date of the last telephone follow up of the last study participant.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Study Participants and Procedures for Enrollment

The goal of this study is to evaluate the long-term safety of open-label treatment (up to 52 weeks per subject) with istradefylline in approximately 300 subjects with moderate to

severe PD who completed double-blind treatment in Study No. 6002-014 for 12 weeks. The enrollment for this study will be those subjects at each site who complete the double-blind study and the 30-day follow-up period and sign consent to continue treatment with open-label istradefylline for up to 52 additional weeks.

A log of all subjects included in the study (i.e., having given informed consent) will be maintained in the Investigator Site File at the investigational site irrespective of whether they have been treated with study drug or not. The reason(s) for exclusion must be recorded.

7.2 Inclusion Criteria

Each subject who meet all of the following inclusion criteria to qualify for entrance into the study:

1) Subjects who have given written informed consent;
2) Subjects who completed 12 weeks of double-blind treatment and the 30-day follow-up period in Study No. 6002-014 ;
3) Subjects who are currently taking levodopa combination (carbidopa/levodopa or benserazide/levodopa) therapy plus at least one adjunctive PD medication.
4) Women of child-bearing potential (WOCBP) must use a reliable method of contraception (e.g., oral contraceptive or long-term injectable or implantable hormonal contraceptive, double barrier methods [such as condom plus diaphragm, condom plus spermicide foam, condom plus sponge], or intra-uterine devices), and must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline.
    a) WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization or is not post-menopausal (defined as amenorrhea $\geq$ 24 consecutive months or a serum follicle-stimulating hormone [FSH] $\geq$ 30 IU/L in the absence of hormone replacement therapy.

7.3 Exclusion Criteria

A subject who meets any of the following exclusion criteria will NOT qualify for the study:

1) Subjects whose treatment compliance was less than 70% throughout their enrollment in Study No. 6002-014;
2) Subjects who are currently treated with apomorphine and/or dopamine receptor antagonists (paliperidone, clozapine, risperidone, olanzapine, quetiapine [except for 100 mg/d or less for levodopa- or PD-induced hallucinations], ziprasidone,

aripiprazole, asenapine, and lurasidone, etc.) or direct gastrointestinal levodopa infusion;

3) Subjects who have been treated within 30 days before Baseline (or five half-lives of the compound, if longer) with any investigational agents other than istradefylline;

4) Subjects who have undergone a neurosurgical procedure for PD (e.g., pallidotomy, thalamotomy, or deep brain stimulation);

5) Subjects who are currently receiving another A_{2A} antagonist (except for caffeine which is allowed);

6) Subjects who are taking potent CYP3A4 inhibitors (systemic antifungals such as ketoconazole);

7) Subjects who are taking potent CYP3A4 inducers (such as St John's Wort and rifampin);

8) Subjects who have had a diagnosis of cancer or evidence of continued malignancy within the past three years (with the exception of adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or in situ prostate cancer with a normal prostate-specific antigen post resection);

9) Subjects with major protocol deviations in Study No. 6002-014 (subjects who failed to meet any of the inclusion criteria, subjects who met any of the exclusion criteria or subjects who met the criteria for subject withdrawal but who were not withdrawn);

10) Subjects who, for any reason, are judged by the Investigator to be inappropriate for this study, including a subject who is unable to communicate or to cooperate with the Investigator or who has/had a clinically significant illness or abnormal physical examination that may compromise the safety of the subject during the study or affect the ability of the subject to adhere to study procedures;

11) Subjects who have clinical laboratory test results that are clinically unacceptable by the Investigator, or who have an alanine aminotransferase and/or an aspartate aminotransferase level > 3 times the upper limit of normal (ULN), and serum total bilirubin > 2 times the ULN at Screening;

12) Subjects who have untreated major depressive disorder;

13) Subjects who have a history of seizures or seizure disorders;

14) Subjects who have a history of neuroleptic malignant syndrome;

15) Subjects with suicidal behavior within the previous month;

16) Subjects who have a history of drug or alcohol abuse or dependence within the last year by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision;

17) Subjects who are pregnant (confirmed by beta human chorionic gonadotropin [β-HCG]), plan to become pregnant, or are breastfeeding.

7.4 Subject Removal (Early Termination)

7.4.1 Subject Removal Criteria

A subject may discontinue from the study at any time. In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Investigator to keep the subject in the study. However, should the subject decide to discontinue treatment, all efforts will be made to complete and report the observations as thoroughly as possible, including a complete final evaluation at the time of the subject's withdrawal with an explanation of why the subject is withdrawing from the study. All subjects who prematurely discontinue from the study will receive a follow-up telephone call one month after discontinuation (refer to Section 9.4.7).

Any of the following circumstances will result in the subject being withdrawn from the study:

- The subject has any clinical AE, laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator (or sub-investigator) that continued participation is not in the best interest of the subject, or if it requires the subject to stop taking levodopa. The Investigator should make a distinction between AEs that may require only interruption of study drug and those that require discontinuation. Subjects experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. If possible, the outcome of any AE that causes permanent discontinuation or that was present at the end of the study should be followed until resolution or return to Baseline condition, particularly if the AE was considered by the Investigator to be related to the study drug;
- The subject requires a concomitant medication that is prohibited in the study;
- The subject wishes to withdraw consent from the study in the absence of a medical need to withdraw as determined by the Investigator;
- The Investigator (or sub-investigator) concludes that it is in the best interest of the subject to discontinue study treatment;
- The subject is noncompliant;
- Administrative reasons; or
- If pregnancy is suspected while the subject is receiving study treatment, the study medication must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study medication will be permanently discontinued and the subject withdrawn from the study. Refer to Section 10.3.2.4 to report any pregnancies.

7.4.2 Subject Removal Procedure

If a subject is withdrawn from the study due to safety concerns such as treatment-emergent adverse events (TEAEs), the Investigator (or sub-investigator) will take appropriate actions for the subject. The Investigator (or sub-investigator) will examine the safety of each withdrawn subject, followed by prompt end-of-study assessments.

A subject who stops visiting the investigative site after exposure to study drug will be followed to the extent possible, in a way that will protect the subject's human rights.

7.4.3 Replacement of Subjects

A subject who withdraws will not be replaced and may not reenter the study.

7.5 Premature Termination or Suspension of the Study at a Specific Investigative Site

If the Investigator prematurely terminates or suspends the study at his or her site due to concerns over the safety of the study drug or for any other reason, the Investigator will promptly notify the Sponsor and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) with a written report describing the premature termination or suspension of the study and the reason for the decision.

Any of the following circumstances as well as the above will result in the premature termination of the study at the site. In such event, appropriate steps will be taken in a similar manner to the above.

- The clinical site requests that the protocol be revised based on the IRB's/IEC's recommendation, but the Sponsor cannot accept the revisions;
- The investigative site's IRB/IEC says that the study should not be continued, and that the study be terminated; or
- The investigative site has major or continuous violations of Good Clinical Practice (GCP), the protocol, or the clinical study agreement.

7.6 Premature Termination or Suspension of the Entire Study

When the entire study needs to be prematurely terminated or suspended, the Sponsor will promptly inform all investigative sites and regulatory agencies with a detailed explanation of

the reason. Upon receipt of such notification, the Investigator will promptly inform the IRB/IEC in writing, with a description of the reason. When the study is prematurely terminated or suspended, the Investigator will promptly brief subjects and take necessary measures such as providing appropriate medical care.

8 TREATMENT OF SUBJECTS

8.1 Study Drug

8.1.1 Study Drug Description

Study drug, istradefylline 20 mg and 40 mg film-coated tablets, will be provided by the Sponsor. The tablets are yellow, plain, round film-coated tablets containing drug substance and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, polyvinyl alcohol, magnesium stearate, film-coating agent, and carnauba wax.

8.1.2 Packaging, and Labelling

Istradefylline tablets will be supplied by the Sponsor in tightly closed, high-density polyethylene bottles (100 tablets per bottle) with child-resistant closures. Study drug will be dispensed at Day 1 (Baseline), at Week 12, and at Week 26. In addition, study drug may be dispensed at unscheduled visits, as necessary.

The bottle label will bear the appropriate text as required by each country's regulatory agency.

8.1.3 Study Drug Accountability and Storage of Study Drug

The Principal Investigator is responsible for maintaining accurate records of the receipt, dispensing, proper storage, and return of all study drug. The Investigator (or designee) may dispense the study drug only to subjects enrolled in the study.

The study drug must be stored at controlled room temperature (20°C to 25°C, [68°F to 77°F]) in a secure location, protected from possible sources of heat, light, or moisture.

Upon completion or termination of the study, all study drug (dispensed and non-dispensed) will be returned to a Sponsor-approved contractor unless other arrangements have been

approved by the Sponsor. The Sponsor will verify that a final report of drug accountability to the unit dose (tablet) level is prepared and maintained in the Investigator's study file.

8.2 Dosage and Administration

8.2.1 Study Drug Administration

The daily dose of istradefylline tablets, 20 mg/d or 40 mg/d will be taken orally in the morning for the duration of study participation on an outpatient basis. Study drug may be taken with or without food.

8.2.2 Antiparkinsonian Medication

All subjects will take their usual daily dose of levodopa combination (levodopa/carbidopa or levodopa/benserazide) therapy. During the study, any change to the established dosage and dosing regimen of concomitant antiparkinsonian medication should be avoided if possible or kept to a minimum. The adjustments are only permitted if subjects experience TEAEs or the clinical response is considered to be unsatisfactory by the Investigator. Consultation with the Medical Monitor is required prior to dose adjustment during the study. All changes made to any medication (either dosage or regimen) must be recorded in the source documents.

8.3 Concomitant Medication

Generic names of all prior and concomitant therapy, including prescription, non-prescription, and supplements, taken by the subject within 30 days prior to the first dose of istradefylline and during the study; within 30 days after the last dose of istradefylline; and anytime thereafter if used to treat study drug-related AEs, will be collected.

8.4 Prohibited Treatment

Medications and treatments listed below are prohibited during the study, and should be avoided for two weeks following the last dose of istradefylline in the study.

1) Apomorphine, and/or dopamine receptor antagonists (paliperidone, clozapine, risperidone, olanzapine, quetiapine, [except for 100 mg/d or less for levodopa- or PD-induced hallucinations], ziprasidone, aripiprazole, asenapine, and lurasidone, etc.)

and/or direct gastrointestinal levodopa infusion (Screening through Week 52/Early Termination [ET]);

2) Any investigational agent (other than istradefylline) within 30 days before Baseline (or five half-lives of the compound, if longer);
3) Any other A_{2A} antagonist;
4) Potent CYP3A4 inhibitors: systemic antifungals, such as ketoconazole;
5) Potent CYP3A4 inducers, such as St John's Wort and rifampin;
6) Any neurosurgical procedure for PD (e.g., pallidotomy, thalamotomy, or deep brain stimulation); and
7) Domperidone.

9 STUDY PROCEDURES

All efficacy and safety measurements obtained during the course of the study are summarized in the Study Schedule of Events (Table 9.4-1).

9.1 Informed Consent

No study procedures may be initiated prior to informed consent being obtained in compliance with International Conference on Harmonisation (ICH)-GCP and local legislation. The participant must personally sign and date the latest approved version of the ICF before any study-specific procedures are performed.

Written and verbal versions of the ICF will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their primary physician, or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorized to do so by the Investigator. A

copy of the signed ICF will be given to the participant. The original signed form will be retained at the study site.

9.2 Dose Assignment

All subjects will be treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at Week 12 based on the Investigator's judgment of each subject's response and tolerability. If deemed necessary, one unscheduled dose adjustment visit between Week 2 to Week 12 is allowed in accordance with clinical judgment of the Investigator. Subjects who had a dose adjustment to 40 mg/d can have their dose decreased to 20 mg/d by the Investigator at a second unscheduled dose adjustment visit if there are tolerability issues. The istradefylline dose should remain fixed between Week 26 to Week 52.

9.3 Blinding/Unblinding

This is an open-label study.

9.4 Procedures

The schedule of study procedures are shown in Table 9.4-1.

Table 9.4-1 Study Schedule of Events

Procedure	Screening[a] Week -1 (Day –7 to -1)	Baseline Day 1	Open-Label Treatment			Follow-up 30 days following Week 52/ET (± 7 days)
			Week 12 (Day 85 ± 4 days)	Week 26 (Day 183 ± 4 days)	Week 52 or ET (Day 365 ± 4 days)	
Written informed consent	X					
Inclusion/Exclusion criteria	X					
Medical history/Demographics	X					
Physical examination	X					
Weight	X					
Height	X					
Vital signs[b]	X					
Clinical laboratory tests	X			X	X	
Serum pregnancy test[c]	X	X[d]	X[d]	X	X	
Serum FSH[e]	X					
12-lead ECG	X					
Concomitant medications	X	X	X	X	X	X[f]
Adverse Events[g]	X	X	X	X	X	X[f]
PGI-I		X[h]	X	X	X	
Treatment compliance			X	X	X	
Dispense study drug		X	X	X		

Note: Visits should occur in the ON state. If possible, subjects should have each visit scheduled for approximately the same time of day from Baseline and onwards.

a: For subjects who have completed 12 weeks of double-blind treatment and the 30-day follow-up period in Study No. 6002-014 immediately prior to entering this study, the Screening Visit for those subjects will correspond to the Follow-up visit of Study No. 6002-014.

b: Vital signs to be measured are blood pressure, heart rate, temperature, and respiration rate; all measurements are to be taken in the ON state.

c: For women of childbearing potential.

d: A urine dipstick pregnancy test will be conducted at Baseline and Week 12.

e: For post-menopausal women only.

f: Subjects will be contacted by telephone for a follow-up visit 30 days (± 7 days) after their last dose of istradefylline.

g: If there are tolerability issues, subjects can be seen at an unscheduled visit in accordance with clinical judgment of the Investigator. At these visits, assessments will include concomitant medications, adverse events, and treatment compliance.

h: Identification only the "key symptom" on the PGI-I (Appendix 1) for subjects.

ECG=electrocardiogram; ET=Early Termination; FSH=follicle stimulating hormone; PGI-I=Patient Global Impression - Improvement Scale

9.4.1 Screening Period (Day -7 to Day -1)

Screening evaluations used to determine the subject's study eligibility must be completed within seven days prior to starting treatment unless otherwise specified. All subjects must

satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections 7.2 and 7.3. The results of all of the Screening and the available Baseline evaluations must be reviewed by the Investigator or his/her designee to ensure that all eligibility criteria have been satisfied prior to the administration of the first dose of istradefylline. For subjects who have completed Study No. 6002-014 immediately prior to entering this trial, the Screening Visit for those subjects will correspond to the Follow-up visit of Study No. 6002-014.

Screening assessments include (Table 9.4-1):

- Written Informed Consent (prior to the conduct of any Screening procedure);
- Confirmation that all eligibility criteria and no exclusion criteria are met;
- Complete medical history with demographics (including age, race, sex, height, weight, daily caffeine intake (number of cups per day [8 ounces] of any caffeinated beverage), current smoking status (number of cigarettes per day);
- Physical examination, which should include general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdominal, musculoskeletal, extremities, lymph nodes, skin, and neurological examinations (cranial nerves, sensory, motor, stance/gait, reflexes, mental status);
- Vital signs (including respiration rate, temperature, blood pressure [BP] and heart rate [HR]) in the ON state;
- Clinical Laboratory Assessments (refer to Table 10.3.3-1 and the Laboratory Manual) including:
  - Hematology Profile;
  - Chemistry Profile;
  - Urinalysis;
  - FSH (post-menopausal women only);
  - Serum Pregnancy test (WOCBP only).

NOTE: For subjects who have completed Study No. 6002-014 immediately prior to entering this study, Visit 12 laboratory assessments will be used as the Screening laboratory assessments.

- 12-lead electrocardiogram (ECG);
- Assessment of AEs (from time of informed consent);
- Assessment of Prior Concomitant Medications (medications taken within 30 days prior to Baseline).

9.4.2 Baseline, Day 1

Baseline will be the first day of istradefylline treatment. Assessments will include (Table 9.4-1):

- Urine dipstick pregnancy test (WOCBP only);
- Identification of only the "key symptom" on the Patient Global Impression - Improvement Scale (PGI-I) (Appendix 1);
- Assessment of AEs;
- Assessment of Concomitant Medications;
- Dispense study drug.

9.4.3 Week 12, Day 85

Subjects will return to the clinic for Week 12 evaluations on Day 85 (± 4 days). Assessments will include (Table 9.4-1):

- Urine dipstick pregnancy test (WOCBP only);
- Assessment of AEs;
- Assessment of Concomitant Medications;
- Score on the PGI-I Scale (Appendix 1);
- Treatment compliance;
- Dispense study drug.

9.4.4 Week 26, Day 183

Subjects will return to the clinic for Week 26 evaluations on Day 183 (± 4 days). Assessments will include (Table 9.4-1):

- Clinical Laboratory Assessments (refer to Table 10.3.3-1 and the Laboratory Manual) including:
  - Hematology Profile;
  - Chemistry Profile;
  - Urinalysis;
  - Serum Pregnancy test (WOCBP only).
- Assessment of AEs;
- Assessment of Concomitant Medications;

- Score on the PGI-I Scale (Appendix 1);
- Treatment compliance;
- Dispense study drug.

9.4.5 Unscheduled Visits

If a subject requires an unscheduled visit for a dose-adjustment or safety/tolerability issues, assessments will include:

- Assessment of AEs;
- Assessment of Concomitant Medications;
- Treatment compliance;
- Dispense study drug.

9.4.6 Week 52, Day 365 / Early Termination

Subjects will return to the clinic for Week 52 evaluations on Day 365 (± 4 days) and any subjects that discontinued istradefylline prior to Week 52 for any reason will undergo the following assessments (Table 9.4-1):

- Clinical Laboratory Assessments (refer to Table 10.3.3-1 and the Laboratory Manual) including:
  - Hematology Profile;
  - Chemistry Profile;
  - Urinalysis;
  - Serum Pregnancy test (WOCBP only).
- Assessment of AEs;
- Assessment of Concomitant Medications;
- Score on the PGI-I Scale (Appendix 1);
- Treatment compliance.

9.4.7 Follow-up Period

Subjects will be contacted by telephone for a follow-up visit 30 days (± 7 days) after their last dose of istradefylline. Any ongoing AEs and SAEs at the last study visit will be followed until there is a return to the subject's Baseline condition, or until a clinically satisfactory

resolution is achieved per the Investigator's judgment. The follow-up assessment will include (Table 9.4-1):

- Assessment of AEs;
- Assessment of Concomitant Medications.

10 EFFICACY, SAFETY, AND OTHER VARIABLES

10.1 Efficacy Assessments

10.1.1 Endpoint

The efficacy variable is change from Baseline in the score on the PGI-I Scale at Weeks 12, 26, and 52.

10.2 Demographics, Medical History, Concomitant Therapy

Subject demographics (race, ethnicity, and sex), caffeine intake (number of cups per day [8 ounces] of any caffeinated beverage), current smoking status (number of cigarettes per day), medical history, and current medical conditions will be recorded at the Screening Visit. Medications taken within 30 days prior to participation in the study will be documented in detail. All relevant medical history, including currently active conditions, diagnosed chronic conditions, and conditions resolved within the past year, will be documented in detail.

Body weight (kg) and height (cm) will be documented during the Screening Visit.

10.3 Safety Assessments

The following information will be collected to evaluate the safety profile of istradefylline in the study population:

- AEs;
- Clinical Laboratory Tests (chemistry, hematology, and urinalysis).

Any clinically important changes noted in vital signs, laboratory tests, or any other potential safety assessments, whether or not these procedures are required by the protocol, must also be collected, when possible, in order for the Sponsor to collect additional information about that

abnormality, including information regarding relationship to the study drug, any action taken, and resolution.

10.3.1 Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug.

The description of each AE will identify the subject, date of onset, the date of resolution, the severity of the event, the action taken regarding study drug, the outcome of the event, and the relationship of the event to study drug. A medical condition present at Screening, but that has increased in frequency or severity, must be collected.

Standard medical terminology should be used to document AEs. The subject's exact description of the event will be recorded in the source documentation. In the case of signs and symptoms, the underlying illness or diagnosis will be recorded as the event when known.

The Investigator will inquire about AEs at all subject visits by asking the subject a non-leading question such as: "How have you been feeling since your last visit?" All AEs, whether observed by the Investigator or reported by the subject, must be collected.

If a subject experiences an AE or SAE, the subject will receive appropriate treatment and supportive care as necessary.

10.3.2 Serious Adverse Events

An SAE is defined as any AE that:

- Results in death.
- Is immediately life-threatening.
  - The term "life-threatening" as part of the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

  - If an event is Grade 4 by Common Terminology Criteria for Adverse Events criteria, it does not necessarily meet the definition for life-threatening as is required for expedited regulatory reporting of SAEs.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is another important medical event. Important medical events are those that may not result in death, be life threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed above.
  - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias that does not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For SAEs, a single term for the diagnosis or underlying illness should be recorded on the SAE Report form; in the event this is unknown, the chief sign/symptom qualifying the event as serious should be recorded.

All AEs, whether non-serious or serious, must be recorded. In addition, any AE that is initially considered serious or becomes serious must be reported.

10.3.2.1 Reporting Procedures for Serious Adverse Events

SAEs require expeditious handling to comply with regulatory requirements. **Any SAE occurring in a clinical study subject must be reported to the Sponsor or designee within 24 hours of the Investigator having knowledge of the SAE.** The Investigator is obligated to immediately report to the Sponsor or designee any SAE occurring at any time after the subject signs the ICF and within 30 days after the last dose of study drug, independent of the circumstances or suspected cause. In addition, the Investigator must promptly report to the Sponsor any SAE occurring at any other time after completion of the study if a causal relationship to study drug is suspected.

SAE reports and follow-up SAE documentation should be forwarded to the Sponsor's Drug Safety Surveillance Department.

SAE FAX US: +1-800-209-2251 or SAE e-mail: saesource@kyowa-kirin-pharma.com

The Investigator or other qualified individual at the investigative site must complete the SAE form and fax or e-mail it to the Sponsor or designee. All telephone communication regarding an SAE must be followed by a written report.

Information must include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality. For all SAEs, the Investigator is obligated to pursue and provide information as requested by the Sponsor in addition to that requested on the SAE form. Supporting documentation such as hospital discharge summaries or lab reports should also be sent to the Sponsor. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor. The Investigator will ensure that information reported immediately by telephone or other means and information entered on the SAE form is accurate and consistent.

The Investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB or IEC. The IRB/IEC must be informed in a timely manner by the Investigator of SAEs occurring at their site during the study. Investigators must also submit safety information provided by the Sponsor to the IRB or IEC.

10.3.2.2 Suspected Unexpected Serious Adverse Reaction Reporting

A suspected unexpected serious adverse reaction (SUSAR) is an AE that meets the serious criteria, is considered related to study drug, and is not identified in nature or severity in the current Investigator's Brochure. All SUSARS will be reported to the relevant Competent Authorities and to the Principal Investigators, who are responsible to notify their respective IRBs/IECs. Principal Investigators will be informed of all SUSARs for the relevant study drug from all studies conducted with the same study drug, and from postmarketing use.

10.3.2.3 Urgent Safety Measures

In accordance with the principles of GCP as laid out in ICH E6, the Investigator(s) has/have primary responsibility for assuring subject safety throughout the performance of study procedures. An urgent safety measure is defined as any measure which an Investigator may need to implement which is a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study subjects without prior IEC/IRB approval/favorable opinion.

The Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical study against any immediate hazards to their health or safety. However, **the Investigator must inform the Sponsor within 24 hours of having taken such measures**.

All urgent safety measures meeting the criteria for an SAE must be reported to the Sponsor using the SAE contact numbers listed in Section 10.3.2.1 within 24 hours of having to take such a measure(s). Such reports can be initiated by telephone but must be officially documented by the Investigator (by email or fax) and must include details of what measures were taken and the circumstances giving rise to those measures.

10.3.2.4 Pregnancy Reporting

When a study subject reports a pregnancy in themselves or their partner (post-study drug administration) to the Investigator, the study drug should be stopped immediately and a pregnancy test should be arranged for the subject (or their partner) by the Investigator within seven days of the pregnancy being reported.

In the case of pregnancy, the Investigator must immediately (within 24 hours of learning of the pregnancy) notify the Sponsor of this event and report the pregnancy on the Pregnancy Surveillance Form. This includes a study subject as well as the partner of a study subject who becomes pregnant while the subject was receiving the study drug. Every attempt will be made to follow the pregnancy to conclusion to obtain information regarding the outcome.

10.3.2.5 Severity

All AEs will be graded as mild, moderate, or severe as defined below:

- Mild– Event results in mild or transient discomfort, not requiring intervention, or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).
- Moderate– Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication).
- Severe– Event results in significant symptoms that prevent normal daily activities; require interventional treatment, and may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

To avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied in Section 10.3.2.

10.3.2.6 Causality

The relationship of each AE to the study drug must be determined by a medically qualified individual according to the following definitions:

- Related: There is a reasonable causal relationship between the study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.
- Not related: An AE that does not follow a reasonable temporal sequence from administration of the study drug or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

10.3.2.7 Collection Period

The collection of AE and SAE information commences following the subject's written consent to participate in the study through the 30-day follow-up period.

10.3.2.8 Acceptable Outcomes

All serious and non-serious AEs must be followed for a final outcome until the end of the follow-up period. The Investigator will continue to closely monitor each subject who experiences an AE (whether ascribed to the study drug or not) until there is a return to the subject's Baseline condition, or until a clinically satisfactory resolution is achieved. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of not resolved is an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study, and for SAEs at database lock.

10.3.3 Assessment of Safety Laboratory Parameters

Clinical laboratory parameters assessed in this study are displayed in Table 10.3.3-1. Any clinically important abnormal laboratory values noted at the Screening visit will be recorded as medical history. If any post-treatment results are judged as being clinically significant by the Investigator, the Investigator should consider whether the result should be recorded as an AE. If deemed necessary, laboratory parameters may be retested or followed as unscheduled tests. Unscheduled tests should be performed by the central laboratory unless immediate results are required for the subject's safety. At minimum, the following laboratory abnormalities should be captured as AEs, as appropriate:

- Any laboratory test result that meets the criteria for a SAE;
- Any laboratory abnormality that requires the subject to have study drug discontinued or interrupted;
- Any laboratory abnormality that requires the subject to receive specific corrective therapy.

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until (1) the value returns to Baseline, (2) the value is judged to be clinically acceptable by the Investigator and the Sponsor, or (3) a diagnosis that explains the abnormal laboratory value is made. When possible, the Investigator should report the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin).

Table 10.3.3-1 Clinical Laboratory Assessments

Serum Chemistry	AST	Creatinine	Chloride
	ALT	Albumin	Total cholesterol
	CK	BUN	Triglycerides
	LDH	Sodium	Uric Acid
	Alkaline phosphatase	Potassium	Amylase
	Total bilirubin	Calcium	Lipase
	Glucose	Serum bicarbonate	Phosphorus
	Total protein		
Hematology	Hemoglobin	WBC	
	Hematocrit	Differential and absolute count	
	RBC	Platelet count	
Coagulation Profile	INR	PT	
Urinalysis (routine or dipstick measurements)	Color	Bilirubin	
	Specific Gravity	Urobilinogen	
	pH	Occult blood	
	Protein	Nitrites	
	Glucose	Microscopic examination, if clinically indicated,	
	Ketones	including RBC, WBC, casts, bacteria, and crystals	
Serum FSH Test	To be performed on all presumed post-menopausal females. Post-menopausal females are defined as females with the complete absence of menses for ≥ 24 consecutive months and a serum FSH level of ≥ 30 IU/L in the absence of hormone replacement therapy		
Serum and/or Urine Pregnancy Test (minimum sensitivity 25 IU/L or equivalent units of β-HCG)	To be performed for all females of childbearing potential.		

ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; β-HCG=beta human chorionic gonadotropin; CK=creatinine kinase; FSH=follicle-stimulating hormone; INR=international normalized ratio; LDH=lactate dehydrogenase; pH=power of hydrogen; PT=prothrombin time; RBC=red blood cells, WBC=white blood cells.

10.3.4 Vital Signs

Vital signs (BP, HR, respiration rate per minute, and temperature) will be measured in the ON state, with the subject in the seated position for at least five minutes, at Screening.

Any new clinically relevant findings that are identified will be reported as AEs.

10.3.5 Electrocardiograms

A standard 12-lead ECG will be performed at Screening. Additional ECGs will be performed only if clinically indicated. ECGs will be conducted after approximately five minutes supine rest using a standard ECG machine equipped with computer-based interval measurements.

The Investigator is responsible for evaluating the ECG interpretation in relationship to clinical signs and symptoms and reaching a medical decision regarding the subject's medical status. The ECG findings should be assessed by the Investigator as normal, abnormal not clinically significant, or abnormal clinically significant, as appropriate. All abnormalities, whether assessed as clinically significant or not, will be recorded. The ECG tracing should be initialed and dated by the Investigator.

10.3.6 Physical Examination

The Investigator will perform a full physical examination at Screening. All abnormal findings will be recorded.

10.4 Appropriateness of Measurements

The safety measurements utilized are considered adequate to determine if istradefylline can be administered safely for 52 weeks.

11 DATA MANAGEMENT

11.1 Source Data

The investigative site Electronic Data Capture (EDC) users will exercise due diligence in ensuring that study data are entered accurately and in their entirety from the investigative site's source documents and flow sheets into the appropriate data entry fields. Only staff

listed on the "Delegation of Authority" page in the Investigator study file and who have been appropriately trained to use the EDC database will be issued a user identification (ID) allowing them to make entries and edits to the EDC database and to respond to queries. Only the Investigator will be issued a user ID allowing the application of an electronic signature to a completed study subject record signifying the data has been reviewed and verified as complete and accurate.

Electronic case report forms, including queries and audit trails, will be retained by the Sponsor.

11.2 Access to Data

Direct access will be granted to authorized representatives from the Sponsor, Contract Research Organization, host institution, and the regulatory authorities to permit study-related monitoring, audits and inspections. The Investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

11.3 Electronic Case Report Forms (eCRFs)

Subject data will be entered into study eCRFs and transmitted electronically to the Sponsor. Management of clinical data will be performed in accordance with applicable industry standards and data cleaning procedures to ensure the integrity of the data. It is the responsibility of the investigative site to prepare and maintain the adequate and accurate eCRFs that have been designed by the Sponsor to record all observations and other data pertinent to the clinical investigation. Electronic CRFs are used to record information collected in the performance of this study and that will be entered into the EDC database. These eCRFs are organized as an ordered series of electronic data entry modules specific for each scheduled and unscheduled study visit.

The Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations.

The Sponsor or designee will be responsible for the processing and quality control of the data. Data management will be carried out by the Sponsor or designee. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

11.4 Record Keeping and Archiving

Electronic CRFs, including queries and audit trails, will be retained by the Sponsor or designee. Study data and other essential documents should be retained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two years have elapsed since the formal discontinuation of clinical development of the study drug. However, these documents should be retained for a longer period if required by the applicable legal requirements. The Sponsor, or its designee, will inform the Investigator, in writing, as to when these documents no longer need to be maintained.

All study documentation at the Investigator's site and Sponsor's site will be archived in accordance with ICH E6-GCP.

11.5 Study Monitoring

Study monitoring will be performed in accordance with ICH E6-GCP, the protocol, and applicable local regulations.

12 STATISTICAL ANALYSIS METHODS

The primary objective of the study is to evaluate the long-term safety and tolerability of oral istradefylline 20 or 40 mg/d as treatment for subjects with moderate to severe PD. Subjects will retain their original identification numbers from Study No. 6002-014.

12.1 Determination of Sample Size

Approximately 300 subjects are anticipated to participate in this study. The sample size was estimated based on the number of subjects anticipated to complete 12 weeks of treatment in Study No. 6002-014 and, of these, the estimated proportion meeting the inclusion/exclusion of this study protocol and the estimated number of eligible subjects who agree to participate.

12.2 Study Endpoints

12.2.1 Safety Endpoints (Primary)

The safety endpoints include the following:

- AEs;
- Clinical laboratory assessments.

12.2.2 Efficacy Endpoint (Secondary)

The efficacy endpoint is defined as:

- Change from Baseline in the score on the PGI-I Scale at Weeks 12, 26, and 52.

12.3 Analysis Populations

The following analysis populations will be used in the study:

1) Intent-to-Treat Set (ITT): Includes all subjects with both a valid Baseline and at least one valid post-baseline assessment.
2) Safety Analysis Set: Includes all subjects who receive at least one dose of assigned study drug (even a partial dose).

12.4 Statistical Analysis

12.4.1 Subject Disposition

Subject disposition will be based on all subjects who are eligible for this study. The number entered, completed, and number discontinuing at each visit will be presented. A summary of reasons for early discontinuation will be provided. Reasons for early discontinuation include AEs, lack of efficacy, protocol violation, or non-compliance with study drug, subject's withdrawal of consent, or other (to be specified by the Investigator). The number of subjects in each of the ITT and Safety Analysis sets will be presented.

12.4.2 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by descriptive statistics based on the ITT and safety populations. These summaries will include demographics (including

age, race, sex, height, weight, daily caffeine intake, smoking status, and BMI), medical history, physical examination results of note, and Baseline PGI-I score. Baseline will be defined as the last observation obtained prior to the first dose of study drug in this study.

12.4.3 Prior and Concomitant Medications

All prior and concomitant medications will be coded to preferred drug names and therapeutic drug class using the World Health Organization Drug Dictionary. The incidence of concomitant medication usage will be summarized for each therapeutic drug class and each preferred drug name. Prior medications will include medications with a documented stop date/time prior to the first dose of study drug. Concomitant medications are those with start date/time on or after the date/time of dosing, or those started prior to the date/time of first dose of study drug but are indicated as continuing into the treatment period. Any medications with partial start and/or stop dates will be considered concomitant if the assignment is uncertain.

12.4.4 Study Drug Exposure and Compliance

The duration of therapy will be summarized as the number of weeks receiving treatment from the first day of dosing to the last day of dosing.

The percent compliance for taking study drug as prescribed will be calculated at Weeks 12, 26, and 52 using the formula:

$$\text{Compliance} = \frac{(\text{Number of tablets dispensed} - \text{Number of tablets returned})}{(\text{Number of tablets expected to be taken})} \times 100$$

Compliance over the entire open-label treatment period will be similarly computed using the total number of tablets dispensed from Baseline to Week 52 and the total number of tablets returned and the total number of tablets expected to be taken for this period. Summary statistics for compliance will be presented for the safety analysis set.

12.4.5 Efficacy Analysis

The efficacy analysis of PGI-I will be based on the ITT population. Actual values and change from Baseline PGI-I values will be summarized at each time point collected using descriptive statistics.

12.4.6 Safety Analyses

The AEs reported during the study will be coded and tabulated by the Medical Dictionary for Regulatory Activities System Organ Class (SOC) and Preferred Term (PT). Treatment-emergent AEs are defined as those AEs with an onset time on or after the start of study drug or are ongoing at the time of study drug initiation and increase in severity or become closer in relationship to study drug during the treatment period. Adverse events with missing start dates will be considered TEAEs. All other AEs will be classified as non-TEAEs and identified in listings only. An overall summary of TEAEs will be presented with the number and percentage of subjects having a TEAE, a serious TEAE, a TEAE leading to study discontinuation, a TEAE with an outcome of death, a TEAE related to study drug, or a severe TEAE.

The overall incidence of TEAEs will be summarized by SOC and PT using the number and percentage of subjects reporting an event and by the number of events reported. TEAEs will also be summarized by maximum severity (mild, moderate, or severe) and closest relationship (related or not related). Serious TEAEs, TEAEs leading to study discontinuation, and TEAEs with an outcome of death will be presented in separate listings.

Descriptive statistics will be provided for actual values and change from Baseline values for clinical laboratory tests (serum chemistry, hematology, and urinalysis) at each assessment time for the Safety Analysis set. Vital signs and physical examination findings will be summarized using actual values at Screening. Screening ECG interpretations will be listed. Clinical laboratory tests categorized as in or out of normal range will be summarized using worst-case shift tables. Worst-case shift tables will be the cross tabulation of the Baseline result category (high, normal, low) with the worst-case result (i.e., out of range: high or low) during the treatment period. Subjects having both an out of range: high and out of range: low laboratory test during treatment will be counted twice in this analysis and flagged accordingly.

All out of normal range results in any safety variable will be flagged in the subject data listings.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Compliance with GCP and Other Applicable Regulatory Requirements

The Investigator will comply with the protocol on which the Investigator and the Sponsor have agreed and which has been approved in writing by the IRB/IEC. The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996, and the current version of the Declaration of Helsinki as well as any applicable national and local laws and regulations. Information regarding any investigational centers participating in this study that cannot comply with these standards will be documented.

The Investigator must not deviate from or change the protocol unless obtaining the Sponsor's prior written agreement and the IRB's/IEC's written approval based on its prior review. In the event of a deviation from or change to the study protocol, the Investigator will make a record of all of the relevant actions regardless of the reason. For medical reasons such as the need to eliminate immediate hazards to the subjects, the Investigator may deviate from or change the protocol without the Sponsor's prior written agreement or the IRB's/IEC's prior written approval. In such case, the Investigator should submit, as soon as possible, a document with a description of the deviation or change and the reason to the Sponsor, and the IRB/IEC to gain their written approval. When the Sponsor amends the protocol, the Sponsor will fully inform each Investigator using the amended version of the protocol or a written description of the amendment to obtain his or her agreement. The Investigator will conduct the study according to the amended protocol after receiving the written approval of the IRB/IEC based on its prior review. However, this does not apply to amendments that only involve administrative issues (e.g., changes in affiliation, job title, address, or telephone number).

Written and oral information about the study in a language understandable by the subject will be given to all subjects. Each subject's willingness to participate in the study will be documented in a signed and dated ICF before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record and the Investigator will sign, date and time the ICF after the subject has signed dated

and recorded the time. The Investigator will keep the original consent forms and copies will be given to the subjects.

13.2 Approvals

The protocol, ICF, participant information sheet and any proposed advertising material will be submitted to an appropriate IEC, regulatory authorities, and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.3 Reporting

The Sponsor or designee will provide regulatory authorities, any central IRB/IEC, and Principal Investigators with safety updates/reports according to local requirements, including SUSARs, where relevant.

Each Principal Investigator is responsible for providing the local IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

13.4 Participant Confidentiality

The Investigator must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In eCRFs and other documents or image material (including materials from all examinations, e.g., X-rays, and ultrasound examinations) submitted to the Sponsor, subjects will not be identified by their names, but by subject identification numbers.

Personal medical information may be scrutinized for the purpose of verifying data recorded in the eCRF. This may be done by the Medical Monitor, properly authorized persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.5 Investigator Information

By signing this protocol, the Investigator recognizes that certain personal identifying information with respect to the Investigator, and all Sub-investigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submission, and as required by law. This information may include:

- name, address, telephone number, and email address
- hospital or clinic address and telephone number
- curriculum vitae or other summary of qualifications and credentials
- other professional documentation

Consistent with the purposes described above, this information may be transmitted to the Sponsor, affiliates, and agents of the Sponsor, in the Investigator's country and other countries, including countries that do not have laws protecting such information. Additionally, the Investigator's name and business contact information may be included when reporting certain SAEs to regulatory agencies or to other Investigators. By signing this protocol, the Investigator expressly consents to these uses and disclosures.

In order to facilitate contact between Investigators, the Sponsor may share an Investigator's name and contact information with other participating Investigators upon request.

13.5.1 Compliance with Law, Audit, and Debarment

By signing this protocol, the Investigator agrees to:

1) Conduct the study in an efficient and diligent manner and in compliance with this protocol, GCP, and all applicable regulatory requirements.
    a) Complete, and/or update Food and Drug Administration (FDA) Form 1572 in a timely manner, and conduct the study in accordance with the specifications on Page 2 of FDA From 1572.
2) Allow monitoring, audits, IRB/IEC review, and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.
    a) Promptly and fully disclose to the Sponsor, and make available at the Investigator's site upon request for inspection all source documentation by representatives of the Sponsor, IRB/IEC, or any regulatory agencies.
    b) Promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

c) The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

3) Provide all data, and upon completion or termination of the clinical study submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

4) Immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened. Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies.

5) The Investigator agrees to provide to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by US FDA regulations (21 Code of Federal Regulations [CFR] Part 54), and other financial regulatory agencies. The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided. This requirement extends to sub-investigators. This may involve the transmission of information to countries that do not have laws protecting personal data.

The ICH E6-GCP guidelines recommend that the Investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

In the event the Sponsor prematurely terminates a particular study site, the Investigator will promptly notify their IRB/IEC.

13.6 Publication Policy

As this study is part of a multicenter study, publications derived from this study should include input from the Investigator(s) and Sponsor personnel. Subsequent to the multicenter publication and according to approved contractual obligations, an Investigator and/or his/her colleagues may publish the results for their study site independently. However, the Sponsor does not recommend separate publication of individual study site results due to scientific concerns.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to

submission. Sponsor review can be expedited to meet publication guidelines. Details of the Sponsor's publication policy can be found in the CTA.

14 QUALITY ASSURANCE

The Sponsor is responsible for Quality Control systems that assure study conduct and data integrity as required by regulatory requirements and GCP as applicable. The Sponsor's Quality Assurance Unit, independent of the Clinical Development function, is responsible for auditing the study.

15 REFERENCES

1. Hauser RA, Shulman LM, Trugman JM, Roberts JW, Mori A, Ballerini R, et al. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. (6002-US-013). Mov disord. 2008;23(15):2177-85.

2. Istradefylline Investigator's Brochure, 16th Edition. Kyowa Hakko Kirin Pharma, Inc.

3. Kondo T, Mizuno Y, Japanese Study Group. A long-term study of istradefylline safety and efficacy in patients with Parkinson's disease (6002-010). Clin Neuropharmacol. 2015 Mar-Apr;38(2):41-6.

4. LeWitt PA, Guttman M, Tetrud JW, Tuite PJ, Mori A, Chaikin P, et al. Adenosine A_{2A} receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). Ann Neurol. 2008; 63(3):295-302.

5. Stacy M, Silver D, Mendis T, Sutton J, Mori A, Chaikin, et al. A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. Neurology. 2008;70:2233-40.

16 APPENDICES/ATTACHMENTS

Appendix 1 Patient Global Impression - Improvement Scale (PGI-I)

Appendix 1 Patient Global Impression - Improvement Scale (PGI-I)

Patient Global Impression - Improvement

Not done ☐

Please rate, in your opinion, how much your overall condition and your specific symptoms have changed since you began taking study medication.

		Improvement
IMPROVEMENT RATING SCALE 1=Moderate Improvement (or greater) 2=Mild Improvement 3=No Change from Baseline 4=Mild Deterioration 5=Moderate Deterioration (or greater)	1. OVERALL CONDITION	
	2. FATIGUE	
	3. SLEEP	
	4. MOTIVATED TO GET TASKS DONE	
	5. KEY SYMPTOM:_____	