CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022075Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022075
Priority or Standard	Class 2 Resubmission
Submit Date(s)	February 27, 2019
Received Date(s)	February 27, 2019
PDUFA Goal Date	August 27, 2019
Division/Office	DNP
Reviewer Name(s)	Natalie Branagan, MD
Review Completion Date	August 26, 2019
Established/Proper Name	Istradefylline
(Proposed) Trade Name	Nourianz
Applicant	Kyowa Kirin Inc
Dosage Form(s)	Tablets
Applicant Proposed Dosing Regimen(s)	Administer 20 mg orally once daily. The dose may be increased to 40 mg once daily based on (b) (4)
Applicant Proposed Indication(s)/Population(s)	Adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "OFF" episodes.
Recommendation on Regulatory Action	There do not appear to be safety concerns that would preclude approval. If efficacy is demonstrated and the benefits of istradefylline outweight the risks, then I recommend that approval include appropriate labeling language addressing any adverse reactions of concerns.
Recommended Indication(s)/Population(s) (if applicable)	Adults

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

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NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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1. Executive Summary

1.1. Product Introduction

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Istradefylline is proposed to be used as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "OFF" episodes. This review evaluates the safety of istradefylline.

Risks:
CNS adverse events (AEs): In the pivotal controlled trials (studies 6002-US-005, 6002-US-013, 6002-009, and 6002-0608), the most common CNS AEs after administration of istradefylline and more common than on placebo were dyskinesias, dizziness, hallucinations, and insomnia. Abnormal thinking and behavior (including one or more of the following: delusions, hallucinations, confusion, mania, agitation, and delirium) were reported at twice the placebo rate (6% vs. 3%) in patients treated with istradefylline 40 mg. Impulse control disorders were also reported in clinical trials (and in the postmarketing setting in Japan, where the drug is already approved).

GI adverse events: Istradefylline is associated with adverse reactions related to nausea, constipation, decreased appetite, and diarrhea, which occurred at a frequency greater than placebo in the pivotal controlled trials.

Analysis and Recommendation with Respect to Safety:
I believe that there are no safety concerns that preclude approval of istradefylline from the clinical safety point of view. If istradefylline is approved, I recommend labeling include Warnings and Precautions statements for CNS effects including dyskinesias, hallucinations, and impulse control disorders. I also recommend a patient labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Please refer to Dr. Kapcala's review of clinical efficacy.	

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Please refer to Dr. Kapcala's review of clinical efficacy.	
Benefit	• Please refer to Dr. Kapcala's review of clinical efficacy.	
Risk and Risk Management	Safety Database The safety database for istradefylline includes all patients from eight Phase 2/3 placebo-controlled trials with Parkinson's disease, five Phase 3 open-label extension studies, five pilot Phase 2 placebo-controlled trials with Parkinson's disease, six placebo-controlled trials for monotherapy with Parkinson's disease or other indications and postmarketing exposure. The clinical trial safety database includes 4,768 subjects, with 1,557 subjects treated for at least 6 months and 1,172 subjects for at least 12 months. The postmarketing database includes an additional 56,000 patients. Safety Concerns • There were 39 deaths in the database. There was not an excess of deaths in istradefylline-treated groups compared to placebo-treated groups in the controlled trials and causes of death were consistent with expected causes of death for the age group and disability caused by Parkinson's disease. • The most common TEAEs in the 4 pivotal controlled trials (studies	The safety database fulfills minimum ICH guidance. Please refer to Dr. Kapcala's review for a summary of current treatment options and safety issues associated with those treatments. Labels for approved dopaminergic agents include warnings for dyskinesias, hallucinations, and impulse control disorders. There were no significant safety findings that would preclude approval of istradefylline. Adequate labeling will address most safety issues with istradefylline. There was an imbalance between istradefylline and placebo in TEAEs related to central nervous system (CNS) effects, including events

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	6002-US-005, 6002-US-013, 6002-009, and 6002-0608) of adjunctive therapy for Parkinson's disease (at least 2% and 2% greater than placebo) were related to dyskinesias, dizziness, hallucinations, insomnia, nausea, constipation, decreased appetite, diarrhea, increased blood alkaline phosphatase, increased blood glucose, increased blood urea, upper respiratory tract infection, and rash. • Abnormal thinking and behavior (including one or more of the following: delusions, hallucinations, confusion, mania, agitation, and delirium) were reported at an incidence of 3% for istradefylline 20 mg, 6% for istradefylline 40 mg, and 3% for placebo. • Impulse control disorders were observed in 1 patient in controlled trials and have been observed in the postmarketing setting in Japan. • Impulse control disorders were observed in 1 patient in controlled trials and have been observed in the postmarketing setting in Japan. • An evaluation of AEs related to ischemia was of interest as istradefylline is an adenosine A2A receptor antagonist and A2A receptors help to regulate coronary blood flow. Overall, the database does not suggest cardiac or ischemic risk. Subjects who received istradefylline had similar incidence of TEAEs belonging to the Cardiac SOC as compared to subjects who received placebo (3.0% versus 3.5%, respectively). Subjects who received istradefylline had similar incidence of TEAEs with potential ischemic etiology as subjects who received placebo (4% versus 5.3%). Increases in mean blood pressure from baseline to a 12-week endpoint were not observed in subjects who received istradefylline in Phase 2/3 controlled clinical trials.	related to dyskinesias and hallucinations. Impulse control disorders have been reported. Warnings and Precautions statements in the labeling could help mitigate risk in patients who have these adverse reactions. An increased incidence of dizziness was also observed and this can be presented in section 6.

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1.4. Patient Experience Data

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala.

2. Therapeutic Context

2.1. Analysis of Condition

This is indicated for adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "OFF" episodes.

2.2. Analysis of Current Treatment Options

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Istradefylline is an adenosine A2A receptor antagonist that is a new molecular entity. It is not currently marketed in the United States. The sponsor received a non-approvable letter in 2008 due to concerns about efficacy. The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala. In the safety review of the original submission by Dr. Gerald Podskalny dated 2/22/2008, dyskinesias, nausea, and dizziness were identified as the most common TEAEs. Adverse events with potential for impulse control disorder were observed as well.

3.2. Summary of Presubmission/Submission Regulatory Activity

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala.

3.3. Foreign Regulatory Actions and Marketing History

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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4.1. Office of Scientific Investigations (OSI)

The reader is referred to the OSI review.

4.2. Product Quality

The reader is referred to the Product Quality review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The reader is referred to the review by Dr. Terry Peters dated 2/28/2008 for the Nonclinical Pharmacology review.

4.5. Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala for a table of clinical studies. For a table of key clinical studies for the safety review, see section 8.1.

5.2. Review Strategy

The clinical review of NDA 022075 is divided into a review of clinical efficacy (by Dr. Leonard Kapcala) and this review of clinical safety. Information submitted as part of NDA 022075 and published literature are discussed in this review. I will primarily present analyses conducted by

myself.

6. Review of Relevant Individual Trials Used to Support Efficacy

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala.

7. Integrated Review of Effectiveness

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala.

8. Review of Safety

8.1. Safety Review Approach

Ten clinical study reports are included in this submission that have not been included in a prior submission: five Phase 1 studies (6002-011, 6002-012, 6002-015, 6002-016, 6002-017), three double-blind, randomized, placebo-controlled Phase 2/3 trials (6002-0608, 6002-009, and 6002-014) and two Phase 3 long-term extension studies (6002-010, 6002-018). An analysis by the sponsor of adverse events from post-marketing data has also been submitted with this submission from approximately 56,000 subjects treated in the post-marketing environment in Japan as of October 31st, 2018.

The integrated safety analysis includes 6 data pools to analyze safety outcomes and are outlined in the below table.

Table 1. Pooled Data for 23 Phase 2/3 Studies.

Pool	Description	Studies	Durations	Doses
1	Double-blind, randomized, placebo-controlled, fixed-dose studies in subjects with Parkinson's disease	6002-US-005 6002-US-006 6002-US-013 6002-US-018 6002-EU-007 6002-0608 6002-009 6002-014	12 or 16 weeks	10, 20, 40, 60 mg/day Placebo: n=1010 Istradefylline: n=2073
2	Open-label, long-term studies	6002-US-007 6002-INT-001	52 or 104 weeks	20, 40, 60 mg/day

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Pool	Description	Studies	Durations	Doses
	in subjects with Parkinson's disease	6002-US-025 6002-010		Istradefylline: n=1893
3	Phase 2 pilot studies in subjects with Parkinson's disease	6002-US-001 6002-US-004 6002-EU04 6002-EU05 6002-0406	Single dose (up to 4, each 2 weeks apart), 4, 6, or 12 weeks	5, 10, 20, 40, 80 mg /day and single doses of 50, 100, 200, and 300 mg Placebo: n=67 Istradefylline: n=149
4	Major Depressive Disorder (N=361), Restless Leg Syndrome (N= 212, PD monotherapy (N=248)	6002-US-101 6002-US-104 6002-US-012 6002-US-201 6002-0407 6002-US-051	4 – 12 weeks	40, 80, 120 mg /day Placebo: n=329 Istradefylline: n=490
S1	Subset of Pool 1: Studies completed after filing of the original NDA	6002-0608 6002-009 6002-014	12 weeks	20, 40 mg/day Placebo: n=449 Istradefylline: n=898
S2	Subset of Pool 1: Studies completed after filing of the original NDA and conducted in Japan.	6002-0608 6002-009	12 weeks	20, 40 mg/day Placebo: n=245 Istradefylline: n=490
8	Double-blind, randomized, placebo-controlled, fixed dose studies in subjects with Parkinson's disease with positive results	6002-US-005 6002-0608 6002-009 6002-US-013	12 weeks	20, 40 mg/day Placebo: n=426 Istradefylline: n=734

Unpooled studies in this submission include six Phase 1 studies (6002-011, 6002-012, 6002-015, 6002-US-026, 6002-016, 6002-017) and one Phase 3 long term study (6002-018). Study 6002-018 was an open-label, flexible-dose study with duration of 52 weeks where subjects were treated with a starting dose of 20 mg daily with option to increase to 40 mg daily at Week 12 based on investigator judgement. The study was completed after the cutoff date for the submission.

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Pools 1 and 2 were comprised of studies where subjects were taking study drug along with levodopa and a DOPA decarboxylase inhibitor (carbidopa or benserazide) for Parkinson's disease. Most subjects in Pool 3 received study drug as adjunctive therapy with levodopa. Subjects enrolled in Study 6002-EU04 of Pool 3 were given study drug as monotherapy for Parkinson's disease. In Pool 4, subjects were given study drug to be used as monotherapy for Parkinson's disease or for other indications.

Reviewer comment: Pool 1 allows for comparison of adverse events between placebo and istradefylline in the key pivotal trials of efficacy. Pool 2 and Study 6002-018 allow for the detection of adverse events occurring in subjects who received istradefylline for a longer period of time. Pool S1 allows for analysis of controlled clinical trials that are new since the original submission. Pool S2 allows for analysis of controlled clinical trials that are new since the original submission and occurred in Japan. I performed an analysis of most frequently reported TEAEs by demographic subgroup which includes an analysis of the incidence of TEAEs reported in Whites and Asians. Analysis of Study 6002-EU04 and Pool 4 allow for analysis of istradefylline-treated subjects who did not have concomitant medication use with levodopa/carbidopa or levodopa/benserazide. Safety Pool 8 allows for evaluation of safety in studies that support the efficacy with istradefylline and are included in labeling.

This review relies primarily upon Pools 1, 8, S1 and S2, as well as the long-term safety data.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The following table shows the overall exposure of istradefylline over the clinical studies database in the current submission.

Table 2. Safety Population, Size, and Denominators

Clinical Trial Groups	Istradefylline	Placebo
New Phase 1 trials (not pooled)	N=163	N=47
Controlled trials conducted for adjunctive therapy for Parkinson's disease (Pool 1)	N=2073	N=1010
Open label trials for adjunctive therapy for Parkinson's disease (Pool 2)	N=1893	NA
Pilot studies conducted for Parkinson's disease (Pool 3)	N=149	N=67
Controlled trials conducted for other indications (Pool 4)	N=490	N=329

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The original NDA submission includes information from 22 Phase 1 studies, and those studies are not included in this submission.

The sponsor also provided safety data on 239 subjects who received istradefylline in the Phase 3 long-term study (6002-018).

The sponsor reports that there were 3,423 subjects who received istradefylline in Phase 2 and Phase 3 clinical studies. Of these subjects, 2,933 received istradefylline as adjunctive treatment for Parkinson's disease.

In Pool 2, 1557 subjects were treated with istradefylline for at least 6 months and 1172 subjects for at least 12 months. The median duration of exposure in Pool 2 was 53.3 weeks.

8.2.2. Relevant characteristics of the safety population:

The following tables show demographics for the safety population for Pool 1 by treatment group. For Pool 1, the population was composed primarily of White and Asian races (69.3% and 27.4%, respectively) with a greater proportion of men than women. Approximately 46% of the population was located outside of North America. The demographics were similar for istradefylline and placebo. The demographics in Pool 1 have a lower percentage of subjects who are female and a lower percentage of subjects that are White compared to the demographics of Parkinson's disease in the United States. A study of Parkinson's disease in U.S. Medicare beneficiaries by Willis et al. showed that 58.3% of the population was female and 86.6% of the population was white. Forty-nine percent were over age 75 years. [1] The higher age in the study compared to Pool 1 may in part be due to selection bias as the study was performed in Medicare beneficiaries.

Table 3. Demographics for Pool 1.

Demographic Parameters	Istradefylline				Placebo N=1010 % (n)	All N=3236 % (n)
	10 mg N=153 % (n)	20 mg N=869 % (n)	40 mg N=896 % (n)	60 mg N=155 % (n)		
Sex						
Male	67.3 (103)	57.5 (500)	58.3 (522)	68.4 (106)	58.2 (588)	59.1 (1912)
Female	32.7 (50)	42.5 (369)	41.7 (374)	31.6 (49)	41.8 (422)	40.9 (1324)
Age (years)						

[1] Willis A., Evanoff B, Lian M, et al. Geographic and Ethnic Variation in Parkinson Disease: A Population-Based Study of US Medicare Beneficiaries. Neuroepidemiology.2010; 34:143-151. DOI 10.1159/000275491.

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Demographic Parameters	Istradefylline				Placebo N=1010 % (n)	All N=3236 % (n)
	10 mg N=153 % (n)	20 mg N=869 % (n)	40 mg N=896 % (n)	60 mg N=155 % (n)		
Mean (SD)	63.2 (8.9)	64.5 (9.0)	63.4 (9.0)	63.5 (10.1)	63.7 (9.0)	63.7 (9.1)
Median	64	65	64	65	64	64
Min, Max	43, 84	35, 87	33, 85	36, 83	36, 87	33, 87
Age Group						
< 65	51.0 (78)	48.7 (423)	52.7 (472)	47.1 (73)	53.4 (539)	51.7 (1672)
>= 65	49.0 (75)	51.3 (446)	47.3 (424)	52.9 (82)	46.6 (471)	48.3 (1564)
< 75	91.5 (140)	86.4 (751)	89.8 (805)	87.1 (135)	88.6 (895)	88.6 (2867)
>= 75	8.5 (13)	13.6 (118)	10.2 (91)	12.9 (20)	11.4 (115)	11.4 (369)
Race						
American Indian or Alaska Native	0	0.4 (3)	0.1 (1)	0	0.1 (1)	0.2 (5)
Asian	2.6 (4)	29.1 (253)	32.8 (294)	1.9 (3)	28.7 (290)	27.1 (877)
Black or African American	2.0 (3)	0.9 (8)	0.3 (3)	3.2 (5)	0.8 (8)	0.8 (27)
Hispanic	2.0 (3)	0.5 (4)	2.2 (20)	2.6 (4)	2.5 (25)	2.2 (71)
Native Hawaiian or other Pacific Islander	0	0.1 (1)	0.1 (1)	0	0	0.1 (2)
Other	0	0.5 (4)	0.5 (4)	0.7 (1)	0.5 (5)	0.5 (17)
White	93.5 (143)	68.6 (596)	64.0 (573)	91.6 (142)	67.4 (681)	69.1 (2237)
Region						
North America	100.0 (153)	61.0 (530)	42.9 (384)	100.0 (155)	50.8 (513)	53.6 (1735)
Outside of North America	0	39.0 (339)	57.1 (512)	0	49.2 (497)	46.4 (1501)
BMI (kg/m^2)						
Mean (SD)	28.5 (5.2)	25.6 (5.1)	25.6 (5.4)	26.3 (4.6)	25.6 (4.9)	25.8 (5.1)
Median	28	25	24.9	25.9	25.5	25.2
Min, Max	18.5, 47.4	15.3, 54.4	13.8, 57.2	15.9, 41.8	14.5, 46.9	13.8, 57.2

This table was created by the reviewer using the ISS dataset ADSL.

Pool S1 was similar to Pool 1 except that there was a higher percentage of females in Pool S1 (49%), a higher percentage of Asians (55%) and a higher incidence of studies occurring outside

of North America (77%).

Pool 8 was similar to Pool 1 with respect to gender and age but was different with respect to race and region. Males made up 50.5% of the population and the median age of the population was 65 years. Asians made up a higher percentage of the population (64.1%). A higher percentage of the population was located outside of North America (63%). Notably, Pool 8 has a higher percentage of subjects with Asian race compared to the general U.S. population with Parkinson's disease.

For all-istradefylline treated subjects in Pool 8, 49.7% were male, 31.7% were White, 67.0% were Asian, 52.9% were ≥65 years of age, 12.7% were ≥75 years of age, and the mean age was 64.5 years.

Pool 2 is notable for the 20 mg group occurring only in studies conducted outside of North America. Additionally, the 20 mg dose group was 100% Asian, had a lower median BMI, and had a higher percentage of female subjects.

Table 4. Demographics for Pool 2.

Demographic Parameters	20 mg N=60 % (n)	40 mg N=1501 % (n)	60 mg N=332 % (n)	All N=1893 % (n)
Sex				
Male	33.3 (20)	61.4 (922)	66.9 (222)	61.5 (1164)
Female	66.7 (40)	38.6 (579)	33.1 (110)	38.5 (729)
Age (years)				
Mean (SD)	65.8 (8.3)	63.1 (9.3)	63.9 (10.0)	63.3 (9.4)
Median	66	63	64.5	64
Min, Max	47, 83	33, 87	36, 87	33, 87
Age Group				
< 65	41.7 (25)	54.4 (816)	50 (166)	53.2 (1007)
>= 65	58.3 (35)	45.6 (685)	50 (166)	46.8 (886)
< 75	88.3 (53)	89.5 (1343)	85.5 (284)	88.8 (1680)
>= 75	11.7 (7)	10.5 (158)	14.5 (48)	11.3 (213)
Race				
American Indian or Alaska Native	0	0.1 (1)	0.3 (1)	0.1 (2)
Asian	100 (60)	23.6 (354)	3 (10)	22.4 (424)
Black or African American	0	0.7 (10)	1.8 (6)	0.9 (16)
Hispanic	0	2.3 (34)	1.5 (5)	2.1 (39)

Demographic Parameters	20 mg N=60 % (n)	40 mg N=1501 % (n)	60 mg N=332 % (n)	All N=1893 % (n)
Native Hawaiian or other Pacific Islander	0	0.1 (2)	0	0.1 (2)
Other	0	0.3 (4)	0.3 (1)	0.3 (5)
White	0	73 (1096)	93.1 (309)	74.2 (1405)
Region				
North America	0	58.8 (883)	100 (332)	64.2 (1215)
Outside of North America	100 (60)	41.2 (618)	0	35.8 (678)
BMI (kg/m^2)				
Mean (SD)	22.3 (3.3)	26.2 (5.2)	26.5 (4.8)	26.1 (5.1)
Median	22.4	25.6	26.0	25.6
Min, Max	15.9, 33.4	14.2, 54.4	15.9, 57.2	14.2, 57.2

This table was created by the reviewer using the ISS dataset ADSL.

The following table shows demographics in study 6002-018. The population was predominately white and was similar to Pool 1 by sex, age, and BMI parameters.

Table 5. Demographics for Study 6002-018.

Demographic Parameters	Istradefylline (20 or 40 mg) N=239 % (n)
Sex	
Male	63.6 (152)
Female	36.4 (87)
Age (years)	
Mean (SD)	65.0 (8.9)
Median	65
Min, Max	40, 86
Race	
Asian	2.1 (5)
Other	0.4 (1)
White	97.5 (233)
BMI (kg/m^2)	
Mean	27.1 (5.0)
Median	26.6
Min, Max	14.2, 42.6

This table was created by the reviewer using Study 6002-018 dataset ADSL

8.2.3. Adequacy of the safety database:

The exposure of the safety database overall appears adequate in terms of size and dosing. The Phase 2/3 studies meet ICH E1A guidelines for exposure at the proposed doses.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The application was well organized and information was easy to find.

8.3.2. Categorization of Adverse Events

The sponsor notes that if a subject was assigned to different doses of istradefylline, the subject's data was assigned to the highest dose received during the study.

The sponsor also notes that if a subject was enrolled in more than one Pool 2 study, the corresponding short-term study data for the istradefylline group subjects was included in the Pool 2 analyses and the data from the same subjects was concatenated (i.e. subjects were not double counted).

The integrated summaries of AEs used MedDRA version 20.0 to classify all AEs reported during the study.

Treatment-emergent AEs were defined in each study SAP or protocol. The following table shows the definition of TEAE by study for Pool 1.

Table 6. Definition of TEAEs by Study for Pool 1.

Study	Definition
6002-US-005 6002-US-006 6002-US-013 6002-US-018 6002-EU-007	AEs that either had an onset time on or after the start of study drug and no more than 14 days (30 days for serious AEs) after the last dose of study drug or were ongoing at the time of study drug initiation and increased in severity or became closer in relationship to study drug during the treatment period.
6002-0608	AEs occurring after exposure to study drug or those which are present before the start of study drug and judged by the investigator to have worsened after exposure to study drug.
6002-014	AEs that either had an onset time on or after the start of study drug or were ongoing at the time of study drug initiation and increased in severity or became closer in relationship to study drug during the treatment period.

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6002-009	AEs that occurred on or after the date of the first dose.

Information from the table was taken from the ISS.

For Pool 2, the sponsor defined TEAEs as those AEs that occurred on or after the date of the first dose of istradefylline including the short-term studies. Per protocol or statistical analysis plan for studies 6002-INT-001, 6002-US-007, and 6002-US-025, SAEs were required to be reported if they occurred during the study or up to 30 days after the last dose of study drug. The protocol and statistical analysis plan for Study 6002-010 did not specify how long SAEs were required to be reported in relation to last dose of study drug.

Per Study 6002-018 protocol, AEs and SAEs were required to be reported within 30 days after the last dose of study drug.

Common TEAEs were defined as the preferred term in which the incidence of any of the istradefylline dose group or the total istradefylline group was > 2% (for the rounded integer) and numerically greater than the placebo incidence (for the rounded integer).

To assess for possible AEs related to stopping istradefylline treatment, including rebound Parkinson's Disease symptoms, the sponsor summarized any AE occurring up to 40 days after the treatment end date (> 5 plasma elimination half-lives) in Pool 1.

Reviewer comment: Variability exists in how TEAEs were defined by study. Presumption of causality by the investigator appears to have played a role in whether AEs were assessed as TEAEs as the investigator had to assess whether an AE worsened in severity after exposure to the study drug. This could cause potential underreporting of TEAEs. The duration of follow up of TEAEs appeared acceptable given that the terminal half-life of istradefylline (82.7 hours).

8.3.3. Routine Clinical Tests

The schedule of assessments for clinical laboratory tests (chemistry, hematology, and urine analysis) were as per the individual study protocols. Seven out of eight studies in Pool 1 had clinical laboratory assessments at baseline (Study Day -1), and then Week 2, 4, 8, and 12. Study 6002-014 had clinical laboratory assessments on Study Days 1, and then Week 2, 6, 10, and 12.

For Pool 2, baseline clinical laboratory assessments occurred between 8 weeks and one day prior to receiving study drug. Subsequent clinical laboratory assessments occurred at Week 2, 4, 6, 8, 12, 20, 28, 36, 44, 48, and 52.

Laboratory results were not normalized for difference reference ranges. Means and changes from baseline were calculated using non-normalized values.

The sponsor used the following criteria to identify potential Hy's law cases:

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- ALT or AST value ≥ 3 x the upper limit of the normal range
- Total Bilirubin value ≥ 2 x the upper limit of the normal range
- Alkaline phosphatase value < 2x the upper limit of the normal range

Reviewer comment: The Agency's Drug Induced Liver Injury: Premarketing Clinical Evaluation Guidance notes that Hy's law cases are cases without initial findings of cholestasis (elevated serum alkaline phosphatase) and the addition of this criteria by the sponsor could make the sponsor's search for Hy's law cases less sensitive.

Vital Signs
For Pool 1 weights were assessed between 8 weeks and one day prior to dosing and then again at week 12. For Pool 2, weights were assessed 8 weeks and one day prior to dosing and also included assessments at 20, 36, and 52 weeks post dosing.

In Pool 1, vital signs were collected at 1 day prior to baseline and then at Week 2, 4, 8, and 12. For Pool 2, vital signs were collected between 8 weeks to one day prior to dosing and then at Week 2, 4, 6, 8, 12, 20, 28, 36, 44, and 52 weeks.

For Pool 1, ECG assessments occurred on Day -1 and then on Weeks 4, 8, and 12. For Pool 2, baseline ECG assessments occurred between 8 weeks and one day prior to dosing, and then on Weeks 4, 8, 12, 20, 36, and 52.

Reviewer comments: Overall, the timing of the assessments of clinical laboratory tests, weights, vital signs, and ECGs appeared adequate.

8.4. Safety Results

8.4.1. Deaths

In placebo-controlled Phase 2b and 3 trials in Pool 1, there was not an excess of deaths in the istradefylline-treated group compared to placebo. Deaths in this submission are consistent with Dr. Podskalny's findings in his review of the original submission that the causes of death in the controlled and open-label studies were consistent with expected causes of death for the age group recruited into the studies and disability caused by PD. As Dr. Podskalny noted in his original review, Poewe[2] reported that the most common causes of death in patients with PD were pneumonia, cardiovascular events, stroke, and cancer.

There were a total of 46 deaths in the program; 33 were reviewed in the first cycle, and I reviewed the last 13 below. Twelve occurred in istradefylline-treated subjects and one occurred

[2] Poewe W. The natural history of Parkinson's disease. J Neurol. 2006 Dec:253 Suppl 7:VII;2-6.

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in a placebo-treated subject.

Of the twelve deaths occurring in istradefylline-treated subjects, one death occurred in Pool 1, six deaths in Pool 2, and five deaths occurred in Study 6002-018 (not pooled).

In Pool 1, there was one additional death occurring in the current cycle in an istradefylline-treated subject in addition to three deaths occurring in istradefylline-treated subjects in the first cycle. There were 4 deaths in subjects who received istradefylline compared to 5 deaths in subjects who received placebo (0.2% (4/2073) versus 0.5% (5/1010), respectively). In the istradefylline group, the TEAEs with outcome of death were: acute cardiac failure, cardiorespiratory arrest, cardiogenic shock, and asthma (each reported in 1 subject). In the placebo group, the TEAEs were pneumonia (n=2), muscle rigidity, intestinal gangrene, sudden death, death, thrombosis mesenteric vessel, and cardio-respiratory arrest. When including the one additional death not included in Pool 1 in this submission (subject (b) (6)), the rate of death in istradefylline-treated subjects remained the same at 0.2% (5/2074).

In Pool 2, there were six additional deaths occurring in the current cycle in istradefylline-treated subjects in addition to the 21 deaths occurring in istradefylline-treated subjects in the first cycle. The death rate was 1.4% (27/1893)). The AEs by preferred term for Pool 2 were pneumonia (n=7), aspiration pneumonia (n=4), Parkinson's disease (n=3), cardiorespiratory arrest (n=2), gastroenteritis (n=2), and myocardial infarction (n=2), acute myeloid leukemia, cardiac arrest, respiratory arrest, respiratory failure, sudden death, abdominal pain upper, vomiting, dehydration, cerebrovascular accident, dizziness, seizure, pelvic fracture, respiratory distress, and intracranial hemorrhage. I reviewed the narratives of cardiac arrest, cardiorespiratory arrest, respiratory distress, respiratory arrest, respiratory failure, and sudden death and note that the subjects had risk factors (such as past medical history) that predisposed them to developing these events.

In Pool 3, there were no additional deaths in the current cycle. In the first cycle, there was one death in a subject who received istradefylline (0.7% (1/149) compared to no deaths in subjects who received placebo. The TEAE of myocardial infarction was associated with the outcome of death in this subject.

There were no deaths in Pool 4.

In study 6002-018, 5 subjects died during the study (2.1% (5/239)). Adverse events associated with fatal outcome were sepsis (n=2), cardiac arrest (n=2), cardiac failure, and acute respiratory failure.

Please see the clinical review from Dr. Gerald Podskalny dated 2/22/2008 for a narrative summary of deaths occurring in the original submission. The following table shows deaths in

subjects who received istradefylline that occurred after the original submission. Due to the presence of comorbidities and underlying risk factors that confounded the cases and adverse events occurring before the AEs of death, I did not find an association with istradefylline and the AEs causing death.

Table 7. Deaths in Istradefylline-treated Subjects that Occurred after the Original Submission.

STUDYID	USUBJID	Age*	Sex	IST Daily Dose	AE onset date**	Preferred Term
Pool 1						
6002-014	(b) (6)	72	M	40 mg	13	Cardiac failure acute
		Risk factors: Arterial hypertension				
Pool 2						
6002-US-025		63	M	60 mg	551	Pneumonia
		Risk factors: Parkinson's disease Other AEs: Hospitalization for right knee surgery, Bronchitis				
6002-US-025		68	M	60 mg	491	Pneumonia Aspiration
		Risk factors: Parkinson's disease Other AEs: Hospitalization for fall with hip fracture, Surgery				
6002-US-025		72	F	60 mg	597	Pneumonia
		Risk factors: Parkinson's disease Other AEs: Hospitalization, Cerebrovascular Accident				
6002-US-025		79	M	40 mg	675	Haemorrhage intracranial
		Risk factors: Aspirin use, Male sex, Age				
6002-US-025		73	M	40 mg	412	Myocardial infarction
		Risk factors: Hypertension, Trifascicular Block, Diabetes Mellitus, History of Pulmonary Embolism				
6002-US-025		81	M	40 mg	464	Cerebrovascular accident
		Risk factors: Age				
Unpooled						
6002-018	(b) (6)	69	M	40 mg	344	Sepsis
		Other AEs: Hospitalization for severe angina pectoris, Bradycardia s/p pacemaker implantation				
6002-018		60	M	40 mg	92	Cardiac failure
		Risk factors: Diabetes mellitus, Hypertension, Hyperlipidemia				

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STUDYID	USUBJID	Age*	Sex	IST Daily Dose	AE onset date**	Preferred Term
6002-018	(b) (6)	65	F	40 mg	268/282	Acute respiratory failure/Cardiac Arrest
		Risk factors: Diabetes mellitus, Hypertension				
6002-018		68	M	40 mg	191	Cardiac arrest
		Risk factors: Diabetes mellitus, Hypertension				
6002-018		72	F	40 mg	378	Sepsis
		Other AEs: Fall, Fracture of Pubic Bone, Urinary Tract Infection				

*Age at time of randomization. **From starting study drug.

I reviewed a case of a death (6002-(b) (6)) occurring in study 6002-018 from acute respiratory failure/cardiac arrest and found a causal role of istradefylline unlikely given the potential contributing factor of drug-induced liver injury occurring in the setting of concomitant paracetamol use.

No deaths occurred in the six Phase 1 studies.

8.4.2. Serious Adverse Events

Consistent with Dr. Podskalny's findings in the original submission, I did not find evidence suggesting a trend for SAEs or specific SAEs in istradefylline-treated subjects that was different from placebo-treated subjects. The frequency of SAEs in the present submission in the controlled clinical trials was similar to that reported in the original submission. Infections and fracture occurred slightly more frequently in istradefylline-treated patients than in placebo, all less than 1%. There were no cases of acute pancreatitis, agranulocytosis, aplastic anemia, bone marrow depression, disseminated intravascular coagulation, hemolytic anemia, pancytopenia, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, or thrombotic thrombocytopenia purpura, in istradefylline-treated subjects.

The following table shows the incidence of any subject experiencing a treatment-emergent SAE by dose in Pool 1. Eighty-seven subjects who received istradefylline reported at least one SAE compared to 31 subjects who received placebo (4.2% versus 3.1%, respectively).

Table 8. Incidence of A Subject Experiencing at Least One Treatment-Emergent SAE by Dose in Pool 1.

10 mg N=153 % (n)	20 mg N=869 % (n)	40 mg N=896 % (n)	60 mg N=155 % (n)	All N=2073 % (n)	Placebo N=1010 % (n)
3.9 (6)	3.9 (34)	4.8 (43)	2.6 (4)	4.2 (87)	3.1 (31)

Reviewer created table from the ISS ADAE dataset with AESER=Y, TRTEMFL=Y, ANL01FL=Y, SAFP01FL=Y.

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grouped on USUBJID and TRP01A.

The following table lists treatment-emergent SAEs (and groupings of closely related SAEs using the ODE-1 methodology) in Pool 1 occurring in at least 2 subjects in an istradefylline dose group and at a rate higher than placebo. Infection and Fracture occurred in 0.8% and 0.5%, respectively, of subjects given istradefylline (doses combined), however; a dose-response was not seen and the difference in incidence from subjects treated with placebo was no greater than 0.4% for these two SAE groupings.

Table 9. Treatment-Emergent Serious Adverse Events Occurring in Pool 1, Grouped Occurring in at Least 2 Subjects and at a Rate Higher Than Placebo.

Serious Adverse Events, grouped	IST 10 mg N=153 % (n)	IST 20 mg N=869 % (n)	IST 40 mg N=896 % (n)	IST 60 mg N=155 % (n)	All IST N=2073 % (n)	Placebo N=1010 % (n)
Infection, all	0.7 (1)	0.9 (8)	0.8 (7)	0.6 (1)	0.8 (17)	0.5 (5)
Fracture	0	0.7 (6)	0.4 (4)	0.6 (1)	0.5 (11)	0.1 (1)
Pneumonia	0.7 (1)	0.3 (3)	0.3 (3)	0.6 (1)	0.4 (8)	0.4 (4)
Fall, dizziness, balance disorder	0.7 (1)	0.3 (3)	0.3 (3)	0.6 (1)	0.4 (8)	0.2 (2)
Fall	0.7 (1)	0.2 (2)	0.3 (3)	0.6 (1)	0.3 (7)	0.2 (2)
Confusion, delirium, altered mental status, disorientation, coma	0	0.2 (2)	0.4 (4)	0	0.3 (6)	0.1 (1)
Arrhythmia: supra-ventricular, AV block, sinus node arrest, pause, block, dysfunction, atrial fibrillation, premature atrial contractions	1.3 (2)	0	0.4 (4)	0	0.3 (6)	0.1 (1)
CHF	0.7 (1)	0.1 (1)	0.3 (3)	0	0.2 (5)	0.1 (1)
Psychosis, delusions, hallucinations	0	0.1 (1)	0.3 (3)	0	0.2 (4)	0
Solid neoplasia, ALL (benign, malignant, unknown)	0	0.3 (3)	0.1 (1)	0	0.2 (4)	0.1 (1)
syncope	0.7 (1)	0.3 (3)	0	0	0.2 (4)	0
Chest pain (non-cardiac or unknown)	0.7 (1)		0.2 (2)	0	0.1 (3)	0.1 (1)

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Serious Adverse Events, grouped	IST 10 mg N=153 % (n)	IST 20 mg N=869 % (n)	IST 40 mg N=896 % (n)	IST 60 mg N=155 % (n)	All IST N=2073 % (n)	Placebo N=1010 % (n)
Cancer (non-squamous cell)	0	0.2 (2)	0.1 (1)	0	0.1 (3)	0
Abdominal pain, distension, bloating, spasm, IBS	0	0.2 (2)	0.1 (1)	0	0.1 (3)	0
UTI	0	0.3 (3)	0	0	0.1 (3)	0
Acute MI	0	0	0.2 (2)	0	0.1 (2)	0
Constipation	0	0.2 (2)	0	0	0.1 (2)	0

Reviewer created table from the ISS ADAE dataset with AESER=Y, TRTEMFL=Y, ANL01FL=Y, SAFP01FL=Y.

The incidence of any subject experiencing a treatment-emergent SAE in Pool 8 was similar to Pool 1. The incidence of any subject experiencing a treatment-emergent SAE by dose in Pool 8 for the 20 mg, 40 mg, and placebo groups was 3.7%, 5.8%, and 2.6%, respectively.

The following table lists treatment-emergent SAEs (and groupings of closely related SAEs using the ODE-1 methodology) in Pool 8 occurring in at least 2 subjects in an istradefylline dose group and at a rate higher than placebo.

Infection occurred in 0.8% of subjects given istradefylline (doses combined), however; a dose-response was not seen and the difference from placebo was no greater than 0.3%.

Table 10. Treatment-Emergent Serious Adverse Events Occurring in Pool 8, Grouped Occurring in at Least 2 Subjects and at a Rate Higher Than Placebo.

Treatment-emergent Adverse Events, grouped	IST 20 mg N=356 % (n)	IST 40 mg N=378 % (n)	All IST N=734 % (n)	Placebo N=426 % (n)
Infection, all	0.8 (3)	0.8 (3)	0.8 (6)	0.5 (2)
Pneumonia	0.3 (1)	0.3 (1)	0.3 (2)	0.5 (2)
Cancer (non-squamous cell)	0.3 (1)	0.3 (1)	0.3 (2)	0
Solid neoplasia, ALL (benign, malignant, unknown)	0.3 (1)	0.3 (1)	0.3 (2)	0.2 (1)

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Treatment-emergent Adverse Events, grouped	IST 20 mg N=356 % (n)	IST 40 mg N=378 % (n)	All IST N=734 % (n)	Placebo N=426 % (n)
Confusion, delirium, altered mental status, disorientation, coma	0.3 (1)	0.3 (1)	0.3 (2)	0
Neuralgia, neuritis, neuropathy	0.3 (1)	0.3 (1)	0.3 (2)	0
EPS, potential EPS, tardive dyskinesia	0.3 (1)	0.3 (1)	0.3 (2)	0
Wheeze, bronchospasm, asthma	0.3 (1)	0.3 (1)	0.3 (2)	0
Gastric, duodenal, or jejunal ulcer, erosion, perforation	0.3 (1)	0.3 (1)	0.3 (2)	0
Chest pain (non-cardiac or unknown)	0	0.5 (2)	0.3 (2)	0
Psychosis, delusions, hallucinations	0	0.5 (2)	0.3 (2)	0
Fracture	0.6 (2)	0	0.3 (2)	0

Reviewer created table from the ISS ADAE dataset with AESER=Y, ANL01FL=Y, studyID=6002-US-005, 6002-0608, 6002-009, 6002-US-013. Grouped by USUBJID, AEDECOD, and TRPO1A.

In Pool 2 (open-label studies), there were 450 subjects who reported at least one SAE (23.8%). The following table shows the incidence of any subject experiencing an SAE by dose in Pool 2.

Table 11. Incidence of A Subject Experiencing at Least One Treatment-Emergent SAE by Dose in Pool 2.

IST 20 mg N=60 % (n)	IST 40 mg N=1501 % (n)	IST 60 mg N=332 % (n)	All N=1893 % (n)
6.7 (4)	25.2 (378)	20.5 (68)	23.8 (450)

Reviewer created table from the ISS ADAE dataset with AESER=Y, TRTEMFL=Y, ANL02FL=Y, SAFP02FL=Y. grouped on USUBJID, and TRP02A.

The following table lists treatment-emergent SAEs (and groupings of closely related SAEs using the ODE-1 methodology) in Pool 2. Infection, Fracture, and Pneumonia occurred in 4.2%, 3%, and 2%, respectively, of subjects given istradefylline. These findings are difficult to interpret in absence of a control group.

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Table 12. Treatment-Emergent Serious Adverse Events with Incidence of at Least 1% Occurring in Pool 2, Grouped.

Serious Adverse Events, grouped	IST 20 mg N=60 % (n)	IST 40 mg N=1501 % (n)	IST 60 mg N=332 % (n)	All N=1893 % (n)
Infection, all	1.7 (1)	4 (60)	5.7 (19)	4.2 (80)
Fracture	1.7 (1)	3.2 (48)	2.1 (7)	3 (56)
Pneumonia	1.7 (1)	1.8 (27)	2.7 (9)	2 (37)
Psychosis, delusions, hallucinations	1.7 (1)	1.9 (29)	0.3 (1)	1.6 (31)
Fall, dizziness, balance disorder	0	1.6 (24)	1.2 (4)	1.5 (28)
Fall	0	1.4 (21)	1.2 (4)	1.3 (25)
Solid neoplasia, ALL (benign, malignant, unknown)	0	1.3 (20)	2.1 (7)	1.4 (27)
Confusion, delirium, altered mental status, disorientation, coma	3.3 (2)	1.4 (21)	1.2 (4)	1.4 (27)
Arthralgia, arthritis, arthrosis	0	1.6 (24)	0.9 (3)	1.4 (27)
Chest pain (non-cardiac or unknown)	0	1.1 (17)	1.2 (4)	1.1 (21)
Pre-syncope or syncope	0	1 (15)	1.2 (4)	1 (19)
CAD, myocardial ischemia, (includes ACS)	0	1.1 (17)	0.6 (2)	1 (19)
Cancer (non-squamous cell)	0	0.8 (12)	1.8 (6)	1 (18)
Sepsis	0	0.1 (2)	1.2 (4)	0.3 (6)
Dysphagia	0	0.1 (1)	1.2 (4)	0.3 (5)
Infection, bacterial	1.7 (1)	0.1 (2)	0.3 (1)	0.2 (4)

Reviewer created table from the ISS ADAE dataset with AESER=Y, TRTEMFL=Y, ANL02FL=Y, SAFP02FL=Y.

In Study 6002-018, 30 subjects reported 64 treatment emergent SAEs. The incidence of a subject reporting at least one treatment-emergent SAE was 12.6% (30/239).

The following table lists treatment-emergent SAEs (and groupings of closely related treatment-emergent SAEs using the ODE-1 methodology) in Study 6002-018. Infection occurred in 2.1% of subjects and Congestive Heart Failure, Arrhythmia, Fracture, and Fall each occurred in 1.3% of subjects. The incidence of the top 5 treatment-emergent SAEs from Study 6002-018 (Infection, Congestive Heart Failure, Arrhythmia, Fracture, and Fall) were similar to Pool 2.

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Table 13. Treatment-Emergent Serious Adverse Events Occurring in Study 6002-018, Grouped.

Serious Adverse Events, grouped	Istradefylline N=239 % (n)
Infection, All	2.1 (5)
Congestive heart failure (CHF)	1.3 (3)
Arrhythmia	1.3 (3)
Fracture	1.3 (3)
Fall	1.3 (3)
Sepsis	0.8 (2)
Pneumonia	0.8 (2)
Urinary Tract Infection (UTI)	0.8 (2)
Cardiac Arrest, Sudden Cardiac Death, Asystole, Electromechanical Dissociation	0.8 (2)
Supra-Ventricular	0.8 (2)
Atrial fibrillation	0.8 (2)
Stroke (Includes Ischemic And Hemorrhagic)	0.8 (2)
Bronchitis, Bronchiolitis, Tracheitis, Alveolitis, Bronchiectasis	0.4 (1)
Cancer (Non-Squamous Cell)	0.4 (1)
Solid Neoplasia, All (Benign, Malignant, Unknown)	0.4 (1)
Angina	0.4 (1)
Pulmonary Edema	0.4 (1)
Coronary Artery Disease, Myocardial Ischemia, (Includes Acute Coronary Syndrome)	0.4 (1)
Arteriosclerosis, Vascular Disease, Peripheral Vascular Disease, Bowel Ischemia	0.4 (1)
Gangrene	0.4 (1)
Conduction Disturbance	0.4 (1)
High Or Third Deg Av Block	0.4 (1)
Av Block	0.4 (1)
Bradycardia	0.4 (1)
Syncope	0.4 (1)
Transient Ischemic Attack (TIA)	0.4 (1)
Dyskinesia	0.4 (1)
Confusion, Delirium, Altered Mental Status, Disorientation, Coma	0.4 (1)
Seizure	0.4 (1)
Anxiety, Nervousness, Panic Attacks	0.4 (1)
Asthenia, Fatigue, Malaise, Weakness, Narcolepsy	0.4 (1)
Elevated Bun or Cr, Anuria, Acute Renal Failure, Chronic renal failure, Oliguria	0.4 (1)
Anemia	0.4 (1)

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Serious Adverse Events, grouped	Istradefylline N=239 % (n)
Apnea, Respiratory Failure, Cyanosis, Hypoxemia, Desaturation, Lung Injury	0.4 (1)
Arthralgia, Arthritis, Arthrosis	0.4 (1)
GOT, GPT, GTP, LFTs	0.4 (1)
Dyspepsia, Nausea, Vomiting, Indigestion, Epigastric Pain, Gastritis, Duodenitis	0.4 (1)
Hernia	0.4 (1)
Diplopia	0.4 (1)
Glaucoma, High Intraocular Pressure	0.4 (1)

Reviewer created table from the Study 6002-018 ADAE dataset with AESER=Y, TRTEMFL=Y, SAFFL=Y.

No treatment-emergent SAEs were reported in the six Phase 1 studies.

Narrative of Select SAE in Pools 1, 2, and Study 6002-018

Abnormal ALT and AST Increase (6002-(b) (6))
72-year-old man with PD and hypertension started treatment with istradefylline 40 mg daily in Study 6002-014. After 43 days of taking istradefylline, the subject experienced increase in ALT (223 U/L with ULN of 44 U/L), AST (766 U/L with ULN 39 U/L), CK (17,431 U/L with ULN 294 U/L), and LDH (899 U/L with ULN 246 U/L). He was asymptomatic at the time (no fever, muscle pain, fatigue or jaundice). His laboratory tests had been normal at Week 2. On Study Day 51, his examination was unchanged and on Study Day 58, his ECG was normal and he was asymptomatic. The event resolved on Study Day 75 without a change in his istradefylline dose (ALT 26 U/L, AST 24 U/L, CK 125 U/L, and LDH 200 U/L). His creatinine, calcium, potassium, bilirubin and alkaline phosphatase levels remained within normal limits and his urine analysis was negative for bilirubin, urobilinogen, protein, or occult blood throughout the study. Myoglobin levels were not measured. Concomitant medication use included entacapone, carbidopa, levodopa, ropinirole, mirtazapine, bisoprolol, amicloton, citalopram hydrobromide, and zolpidem.

Reviewer comment: Elevation of CPK, ALT, AST, and LDH suggest possible rhabdomyolysis; however, the subject was asymptomatic which is uncharacteristic of rhabdomyolysis. A role for istradefylline in the event of elevation of CPK, ALT, AST, and LDH cannot be ruled out although it is unlikely as the event resolved without a change in the dose of the medication. Additionally, potential confounding factors exist in this case including concomitant medication use with levodopa/carbidopa/entacapone and citalopram as side effects on their labeling include risk for rhabdomyolysis.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The following tables show subject disposition for Pools 1 and 2. In Pool 1, the rates for

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discontinuations due to adverse events were greater for istradefylline-treated subjects than placebo with evidence of a dose response. In Pool 2, a higher incidence of subjects discontinued due to AEs (14.5%) and may in part be due to the longer duration of the studies (median duration of 53.3 weeks). The sponsor terminated studies 6002-US-007 and Study 6002-US-025 which also led to a lower completion rate in Pool 2.

Table 14. Subject Disposition for Pool 1.

Disposition	IST 10 mg N = 153 % (n)	IST 20 mg N=869 % (n)	IST 40 mg N=896 % (n)	IST 60 mg N=155 % (n)	ALL IST N=2073 % (n)	Placebo N=1010 % (n)
Adverse Event	3.3 (5)	5.5 (48)	7.5 (67)	10.3 (16)	6.6 (136)	5.4 (55)
Completed	88.9 (136)	90.4 (786)	89.4 (801)	81.3 (126)	89.2 (1849)	89.8 (907)
Death	0.7 (1)	0	0.3 (3)	0	0.2 (4)	0.5 (5)
Lack of efficacy	1.3 (2)	0.2 (2)	0.3 (3)	1.3 (2)	0.4 (9)	0.5 (5)
Non-compliance with study drug	0	0	0.3 (3)	0	0.1 (3)	0.2 (2)
Other	0	0.2 (2)	0.2 (2)	1.9 (3)	0.3 (7)	0.3 (3)
Physician Decision	0	0.3 (3)	0	0	0.1 (3)	0.3 (3)
Protocol Deviation	2.6 (4)	0.9 (8)	0.1 (1)	3.2 (5)	0.9 (18)	0.6 (6)
Screen Failure	0	0.1 (1)	0.1 (1)	0	0.1 (2)	0.1 (1)
Withdrawal by subject	3.9 (6)	2.2 (19)	1.9 (17)	1.9 (3)	2.2 (45)	2.8 (28)

The reviewer created this table from the ISS Dataset ADSL.

Table 15. Subject Disposition for Pool 2.

Disposition	IST 20 mg N=60 % (n)	IST 40 mg N=1501 % (n)	IST 60 mg N=332 % (n)	ALL IST N=1893 % (n)
Adverse Event	15 (9)	15.5 (232)	10.2 (34)	14.5 (275)
Completed	66.7 (40)	39.5 (593)	3.6 (12)	34.1 (645)
Death	0	1.3 (19)	2.4 (8)	1.4 (27)
Lack of efficacy	0	7.1 (106)	11.1 (37)	7.6 (143)
Other*	5 (3)	28.6 (430)	67.5 (224)	34.7 (657)
Physician Decision	5 (3)	1 (15)	0	1 (18)
Protocol Deviation	0	0.8 (12)	1.5 (5)	0.9 (17)
Withdrawal by subject	8.3 (5)	7.5 (113)	6 (20)	7.3 (138)

The reviewer created this table from the ISS Dataset ADSL. *Other includes discontinuations of subjects due to sponsor's decision to terminate studies 6002-US-007 and Study 6002-US-025.

Pool 8 had similar rates of discontinuation due to adverse events as Pool 1. The following table

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shows subject disposition for Pool 8.

Table 16. Subject Disposition for Pool 8.

Disposition	IST 20 mg N=356 % (n)	IST 40 mg N=378 % (n)	All IST N=734 % (n)	Placebo N=426 % (n)	All N=1160 % (n)
Adverse Event	5.1 (18)	6.1 (23)	5.6 (41)	4.7 (20)	5.3 (61)
Completed	90.2 (321)	90.2 (341)	90.2 (662)	89 (379)	89.7 (1041)
Lack of Efficacy	0 (0)	0.3 (1)	0.1 (1)	0.2 (1)	0.2 (2)
Non-Compliance with Study Drug	0 (0)	0.3 (1)	0.1 (1)	0.5 (2)	0.3 (3)
Other	0.3 (1)	0 (0)	0.1 (1)	0 (0)	0.1 (1)
Physician Decision	0.8 (3)	0 (0)	0.4 (3)	0.7 (3)	0.5 (6)
Protocol Deviation	1.1 (4)	0.3 (1)	0.7 (5)	0.5 (2)	0.6 (7)
Withdrawal by Subject	2.5 (9)	2.9 (11)	2.7 (20)	4.5 (19)	3.4 (39)

The reviewer created this table from the ISS Dataset ADSL.

In study 6002-018, adverse events lead to discontinuations in 10.5% of the safety population, which was a similar rate as Pool 2.

In Pool 1, the most frequently reported TEAEs leading to discontinuation were Nausea/Vomiting and Psychosis/Delusions/Hallucinations, and each led to discontinuation in 0.4% of subjects given istradefylline (all doses combined). These TEAEs were among the most frequently reported TEAEs in Pool 1. In Dr. Podskalny's review, dyskinesias, worsening Parkinson's symptoms, and nausea were the most common adverse events associated with discontinuation. Psychosis/Delusions/Hallucinations causing discontinuations in the current submission compared to the original submission may be due to the difference in populations between the submission. The absence of worsening Parkinson's symptoms in this submission may be due to differences in efficacy from the additional trials in this submission.

In Pool 2, the most frequently reported TEAEs leading to discontinuation were Psychosis/Delusions/Hallucinations, Dyskinesias, and Solid Neoplasia which occurred in 2.3%, 1.5%, and 1.2%, respectively of subjects. These TEAEs were among the most frequently reported TEAEs in Pool 2.

In Study 6002-018, Dyskinesia and Infection were the most frequently reported TEAEs leading to discontinuation and occurred in 1.7% and 1.3%, respectively, of subjects.

In Pool 8, hallucinations (including visual, olfactory, somatic, and auditory hallucinations) caused 1% of patients randomized to istradefylline 40 mg to discontinue, compared to 0% for istradefylline 20 mg and for placebo. Dyskinesias caused 1% in the 20 mg and 40 mg dose arms to discontinue compared to 0% in the placebo arm in Pool 8.

8.4.4. Significant Adverse Events

The following tables shows severity of TEAEs in Pools 1 and 2. In Pool 1, 6.5% of TEAEs occurring in subjects who received istradefylline were severe compared to 6.0% of TEAEs occurring in subjects who received placebo. Pool 2 had a similar percentage of TEAEs categorized as severe as compared to Pool 1. In Pool 2, a dose response is observed for severe events. In Study 6002-018, the incidence of severe TEAEs was 8.9%.

Table 17. Severity of TEAEs Pool 1.

TEAE Severity	IST 10 mg N = 418 %	IST 20 mg N=1825 %	IST 40 mg N=1970 %	IST 60 mg N=436 %	ALL IST N=4649 %	Placebo N=1944 %
Mild	52.9	62.7	61.5	57.6	60.9	63.5
Moderate	40.9	30.6	32.4	34.9	32.7	30.5
Severe	6.2	6.6	6.1	7.6	6.5	6

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y. The denominator is the total number of TEAEs experienced per dose.

Table 18. Severity of TEAEs Pool 2.

TEAE Severity	IST 20 mg N=276 %	IST 40 mg N=13932 %	IST 60 mg N=3536 %	ALL IST N=17744 %
Mild	89.9	54.5	51	54.3
Moderate	9.1	38.5	41.4	38.6
Severe	1.1	7	7.6	7

Reviewer created table from the ISS ADAE dataset with ANL02FL=Y, SAFP02FL=Y. The denominator is the total number of TEAEs experienced per dose.

Table 19. Subject Disposition for Study 6002-018.

TEAE Severity	Istradefylline (20 or 40 mg) N=239 %
Mild	42.3
Moderate	35.1
Severe	11.3

Reviewer created table from Study 6002-018 ADAE dataset with TRTEMFL=Y, SAFFL=Y. Grouped by USUBJID,

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AESEV and TRTA. Subjects could experience more than one TEAE.

There were two cases of megacolon occurring in Pool 2 and I summarize the cases here.

Megacolon (6002-US[redacted], USUBJID [redacted] in the original submission)
77-year-old male with history of Parkinson's disease, hypothyroidism, mitral valve prolapse, fluid retention, left bundle branch block, reflux, dizziness, hallucinations, falls, hypertension, hypersomnolence who developed diarrhea and abdominal cramps on Study Day 189 of the open label extension study (6002-US-007). Two days later, his abdomen was rigid and distended and a day later, he was admitted to the hospital. He was found to have megacolon with distention greater than 15 cm in multiple areas of the bowel, categorized as severe. He underwent an exploratory laparotomy and was found to have a sigmoid volvulus. A total abdominal colectomy was performed and he was placed on total parenteral nutrition as well as tube feeds through a nasogastric tube. A gastrostomy tube was unable to be placed due to angulation of the stomach and he was discharged to a long-term acute care facility. Concomitant medications included levothyroxine, diphenhydramine, ropinirole, entacapone, Dyazide, triamcinolone inhaled, multivitamin, potassium supplement, vitamin E supplement, and ascorbic acid. On Study Day 244, he developed worsening dysphagia and underwent placement of a gastrostomy tube. The subject withdrew consent and was withdrawn from treatment on Study Day 252.

Reviewer comment: A role for istradefylline in the event of megacolon cannot be ruled out as the event occurred while the subject was taking the medication. Additionally, constipation is one of the most common TEAEs reported with istradefylline. Potential contributing factors to the case include the subject's history of hypothyroidism. Potential confounding factors include the use of concomitant medications including diphenhydramine, ropinirole, entacapone, and Dyazide.

Megacolon (6002-US-[redacted], USUBJID [redacted] in the original submission)
78-year-old man with history of hypothyroidism, coronary artery disease, chronic cardiac failure, myocardial infarction, basal cell carcinoma, melanoma, hypertension, reflux disease, recurrent prostate cancer, peripheral neuropathy, memory loss, hypertonic bladder who developed megacolon, mild in severity, that occurred on Study Day 120. The AE resolved by Study Day 165. Further details of the AE of megacolon are lacking. Concomitant medication use included levodopa, carbidopa, entacapone, gabapentin, colesevelam, esomeprazole, levothyroxine, acetylsalicylic acid, quetiapine, ropinirole, lisinopril, nitrofurantoin, and warfarin. Within a week of his diagnosis with megacolon, he had an elevated creatinine of 3.1 mg/dL (ULN 1.5 mg/dL), low hematocrit of 28% (LLN 37%), and had been hospitalized for anemia with treatment of 4 units of packed red blood cells per day from study Day 119 to 125. On Study Day 125, he was discharged to a hospice care facility (creatinine at the time was 2.3 mg/dL). The last dose of study drug was on Study Day 147. On Study Day 148, he was diagnosed with renal

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insufficiency secondary to dehydration. The anemia was thought to be secondary to his renal insufficiency and he was treated with erythropoietin. On Study Day 160, he developed community acquired pneumonia and died on Study Day 165.

Reviewer comment: A role for istradefylline in the event of megacolon cannot be ruled out as the event occurred while the subject was taking the medication. Additionally, constipation is one of the most common TEAEs reported with istradefylline. Potential contributing factors to the case include the subject's history of hypothyroidism. Potential confounding factors include the use of concomitant medications including levodopa, carbidopa, entacapone, ropinirole, and esomeprazole.

Overall, a role for istradefylline in the cases of megacolon cannot be established due to the presence of confounding factors in the cases.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The following table shows the incidence of any subject experiencing at least one TEAE by dose in Pool 1. At least one TEAE was reported in 72.4% of all subjects treated with istradefylline compared to 65.4% of subjects treated with placebo. The most commonly reported TEAEs in Pool 1 were dyskinesias.

Table 20. Incidence of A Subject Experiencing at Least One TEAE by Dose in Pool 1.

IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
82.4	70.7	70.1	85.8	72.4	65.4

Reviewer created table from the ISS ADAE dataset with TRTEMFL=Y, ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A.

The following table lists TEAEs (and groupings of closely related TEAEs using the ODE-1 methodology) in Pool 1. Dyskinesias, Fall/Dizziness/Balance Disorder/Gait Disturbance/Difficulty Walking, and Dyspepsia/Nausea/Vomiting/Indigestion/Epigastric Pain/Gastritis/Duodenitis occurred in 17.8%, 11.9%, and 9.2%, respectively, of subjects given istradefylline (doses combined), however; a dose-response was not seen. These TEAEs were similar to the most frequently reported TEAEs in the safety review by Dr. Podskalny. A dose-response was seen with Dry Mouth/Dry Lips/Thirst in istradefylline-treated subjects; however, the overall incidence of TEAEs belonging to the grouping is low (1.1%).

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Table 21. Treatment-Emergent Adverse Events with an Incidence of At Least 2% and at Least 1% Greater than Placebo Occurring in Pool 1, Grouped.

Treatment-emergent Adverse Events, grouped	IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
Dyskinesia	21.6	16.1	17.7	23.9	17.8	9.6
Fall, Dizziness, Balance Disorder, Gait Disturbance, Difficulty Walking	15	11.2	10.8	20.6	12	9.6
Fall, Dizziness, Balance Disorder	14.4	11.2	10.7	20.6	11.9	9.5
Dizziness	5.2	5.1	4.9	14.2	5.7	4.2
Dyspepsia, Nausea, Vomiting, Indigestion, Epigastric Pain, Gastritis, Duodenitis	11.8	7.4	8.1	23.2	9.2	6.2
Insomnia, Sleep Disturbance, Abnormal Dreams	11.8	7.9	8.7	11.6	8.8	5.5
Nausea, Vomiting	7.2	6.4	6.7	22.6	7.8	4.9
Abdominal Pain, Distension, Bloating, Spasm, IBS	9.2	7	7.7	5.8	7.4	5.2
Uri, Cold, Rhinitis, Upper Resp Tract Infection, Flu-Like Illness	9.8	6.2	7.1	7.1	6.9	6.9
Dizziness, Light-Headedness	5.2	5.1	4.9	14.2	5.7	4.2
Constipation	6.5	5.8	5.4	1.9	5.4	3.3
Insomnia	6.5	4	5.9	3.2	5	4.4
Somnolence, Fatigue, Sedation	7.2	5.3	4	4.5	4.8	4.9
Psychosis, Delusions, Hallucinations	3.9	3.5	4.9	7.7	4.4	2.5
Asthenia, Fatigue, Malaise, Weakness, Narcolepsy	5.9	2.8	3.3	3.9	3.3	3.2
Arthralgia, Arthritis, Arthrosis	6.5	2.3	2.9	7.7	3.3	3.6

Treatment-emergent Adverse Events, grouped	IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
Anxiety, Nervousness, Panic Attacks	3.3	2.4	3	5.2	2.9	2.3
Cramps, Muscle Spasm	3.9	1.5	1.1	3.9	1.7	1.3
Paresthesia, Hypoaesthesia	1.3	1.6	1.6	2.6	1.6	0.4
Dry Mouth, Dry Lips, Thirst	0	0.6	1.3	3.2	1.1	0.8
Visual Disturbance	0.7	1	0.4	2.6	0.9	0.3
Rash, Eruption, Dermatitis	3.3	1.4	1.6	1.9	1.6	1.2
Confusion, Delirium, Altered Mental Status, Disorientation, Coma	5.9	4.5	2.8	5.2	3.9	4
Headache	5.2	3.1	3.7	5.2	3.7	3.3
UTI	3.3	2.6	2.9	1.3	2.7	2.4
CPK Increased	0.7	2.4	2.3	3.9	2.4	2.7
Orthostasis	1.3	3.3	0.8	1.9	2	1.4
Depression	0	1.6	1.3	3.2	1.5	2
Anorexia, Decreased Appetite	1.3	1.4	1.6	2.6	1.5	1.3
Fracture	2	2	1.1	0.6	1.5	0.9
Chest Pain (Non-Cardiac Or Unknown)	2.6	1.4	1.3	0.6	1.4	1.4
Neuralgia, Neuritis, Neuropathy	2	0.7	0.7	0.6	0.8	0.3
Gait Disturbance, Difficulty Walking,	2	0.5	1	0.6	0.8	0.5
Polyuria, Increased Frequency	2	0.5	0.4	1.3	0.6	0.3
Myalgia	2	0.2	0.8	0.6	0.6	0.7

Reviewer created table from the ISS ADAE dataset with TRTEMFL=Y, ANL01FL=Y, SAFP01FL=Y, grouped by USUBJID, AEDECOD, and TRPO1A.

The following table shows the incidence of any subject experiencing at least one TEAE by dose in Pool 2. At least one TEAE was reported in 92.4% of all subjects treated with istradefylline.

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Table 22. Incidence of A Subject Experiencing at Least One TEAE by Dose in Pool 2.

IST 20 mg N=60 %	IST 40 mg N=1501 %	IST 60 mg N=332 %	All N=1893 %
93.3	91.7	95.5	92.4

Reviewer created table from the ISS ADAE dataset with TRTEMFL=Y, ANL02FL=Y, SAFP02FL=Y. grouped on USUBJID, and TRP02A.

The following table lists TEAEs (and groupings of closely related TEAEs using the ODE-1 methodology) in Pool 2. Infection, Dyskinesia, and Fall/Dizziness/Balance Disorder occurred in 38.6%, 38.4%, and 31.0%, respectively, of subjects.

Table 23. Treatment-Emergent Adverse Events with an Incidence of At Least 4% Occurring in Pool 2, Grouped.

Treatment-Emergent Adverse Events, grouped	IST 20 mg N=60 %	IST 40 mg N=1501 %	IST 60 mg N=332 %	All IST N=1893 %
Infection, All	36.7	37.9	41.9	38.6
Dyskinesia	28.3	38	41.9	38.4
Fall, Dizziness, Balance Disorder, Gait Disturbance, Difficulty Walking	3.3	28.2	49.1	31.1
Fall, Dizziness, Balance Disorder	3.3	28	49.1	31
Insomnia, Sleep Disturbance, Abnormal Dreams	11.7	23.4	40.7	26
Abdominal Pain, Distension, Bloating, Spasm, Irritable Bowel Syndrome (IBS), Megacolon	3.3	21.4	25.9	21.6
Uri, Cold, Rhinitis, Upper Resp Tract Infection, Flu-Like Illness	20	20.6	21.1	20.7
Dyspepsia, Nausea, Vomiting, Indigestion, Epigastric Pain, Gastritis, Duodenitis	5	16.6	28.6	18.3
Psychosis, Delusions, Hallucinations	15	17.3	18.1	17.4
Insomnia	6.7	15.9	22.3	16.7
Fall	1.7	15.7	21.7	16.3
Constipation	1.7	16.4	18.4	16.3
Nausea, Vomiting	3.3	12.5	27.1	14.7
Infection, Viral	20	14.9	10.2	14.3
Somnolence, Fatigue, Sedation	8.3	13.3	17.5	13.9

Treatment-Emergent Adverse Events, grouped	IST 20 mg N=60 %	IST 40 mg N=1501 %	IST 60 mg N=332 %	All IST N=1893 %
Confusion, Delirium, Altered Mental Status, Disorientation, Coma	11.7	12.6	19	13.7
Arthralgia, Arthritis, Arthrosis	8.3	13.7	14.2	13.6
Dizziness, Light-Headedness	1.7	10.5	27.7	13.2
Asthenia, Fatigue, Malaise, Weakness, Narcolepsy	0	12.9	14.5	12.8
Anxiety, Nervousness, Panic Attacks	1.7	11.1	10.2	10.6
Depression	1.7	10.2	13.9	10.6
Edema, Non-Pulmonary, Fluid Retention, Overload	1.7	9.7	11.7	9.8
UTI	10	9	9.9	9.2
Headache	0	7.6	12.7	8.2
Tremor, Shakiness, Trembling	0	8.5	8.4	8.2
Fracture	10	8.2	6.3	7.9
Weight Loss, Catabolic State, Cachexia, Failure To Thrive	5	8.5	5.1	7.8
Diarrhea, Colitis, Enteritis, Proctitis, Gastroenteritis, C-Diff	3.3	7.3	10.2	7.7
Cramps, Muscle Spasm	0	6.7	5.4	6.3
Chest Pain (Non-Cardiac Or Unknown)	1.7	6.5	4.5	6
Eps, Potential Eps, Tardive Dyskinesia	0	4.4	9.6	5.2
Solid Neoplasia, All (Benign, Malignant, Unknown)	0	4.6	7.5	5
Hypertension, Bp Increased	1.7	5.1	3.3	4.7
Dyspnea, Sob, Respiratory Distress	0	4.3	6.6	4.5
Arrhythmia	6.7	4.3	4.8	4.5
Cough	1.7	4.5	4.8	4.4
Bleeding	0	4.5	3.9	4.3
Anorexia, Decreased Appetite	3.3	3.3	8.1	4.2
Orthostasis	0	3.8	6.6	4.2
CPK Increased	0	4.4	3.3	4.1
Vertigo; Vestibular Dysfunction	3.3	4.4	2.1	4
Rash, Eruption, Dermatitis	3.3	3.5	5.7	3.9
Reflux, Gerd	1.7	3.9	4.2	3.9
Pre-Syncope Or Syncope	0	3.7	4.8	3.8
Memory Loss, Impairment	0	3.4	5.4	3.6

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Treatment-Emergent Adverse Events, grouped	IST 20 mg N=60 %	IST 40 mg N=1501 %	IST 60 mg N=332 %	All IST N=1893 %
Visual Disturbance	0	3.5	4.5	3.5
Syncope	0	3.5	4.2	3.5
Pneumonia	1.7	3.4	4.2	3.5
Eye Other	5	3.7	1.8	3.4
Infection, Fungal	5	3.7	1.5	3.3
Diabetes, Glucose Intolerance, Hyperglycemia, Hba1C, Glycosuria, Ketones	8.3	3.3	1.5	3.1
Restlessness, Agitation, Hyperkinesia, Akathisia	0	2.5	5.7	3
Paresthesia, Hypoaesthesia	0	2.6	4.8	2.9
Dysphagia	0	2.4	4.5	2.7
Supra-Ventricular	5	1.7	2.1	1.8
Infection, Bacterial	5	1.4	1.5	1.5
GOT, GPT, GPTP, LFTs	6.7	1.7	1.5	1.8
Eczema	10	1.1	0	1.2

Reviewer created table from the ISS ADAE dataset with TRTEMFL=Y, ANL02FL=Y, SAFP02FL=Y, grouped by USUBJID, AEDECOD, and TRPO2A.

In Study 6002-018, the incidence of a subject reporting at least one TEAE was 59.0% (141/239).

The following table lists TEAEs (and groupings of closely related TEAEs using the ODE-1 methodology) in Study 6002-018. Dyskinesia, Fall/Dizziness/Balance Disorder, and Infection occurred in 43%, 35%, and 29%, respectively, of subjects.

Table 24. Treatment-Emergent Adverse Events with an Incidence of At Least 2% Occurring in Study 6002-018, Grouped.

Treatment-Emergent Adverse Events, grouped	Istradefylline N=239 %
Dyskinesia	18
Fall, Dizziness, Balance Disorder	14.6
Infection, All	12.1
Fall	12.1
Insomnia, Sleep Disturbance, Abnormal Dreams	7.1
Arthralgia, Arthritis, Arthrosis	6.3

Treatment-Emergent Adverse Events, grouped	Istradefylline N=239 %
Abdominal Pain, Distension, Bloating, Spasm, Irritable Bowel Syndrome	5.9
Confusion, Delirium, Altered Mental Status, Disorientation, Coma	4.6
Psychosis, Delusions, Hallucinations	4.6
Somnolence, Fatigue, Sedation	4.2
Anxiety, Nervousness, Panic Attacks	4.2
Insomnia	4.2
Dizziness, Light-Headedness	4.2
Asthenia, Fatigue, Malaise, Weakness, Narcolepsy	4.2
Constipation	4.2
Dyspepsia, Nausea, Vomiting, Indigestion, Epigastric Pain, Gastritis, Duodenitis	4.2
Fracture	4.2
UTI	3.8
Edema, Non-Pulmonary, Fluid Retention, Overload	3.8
Depression	3.8
Uri, Cold, Rhinitis, Upper Resp Tract Infection, Flu-Like Illness	2.9
Headache	2.9
Anemia	2.9
Nausea, Vomiting	2.9
Negative Symptoms	2.5
Tremor, Shakiness, Trembling	2.5
Bronchitis, Bronchiolitis, Tracheitis, Alveolitis, Bronchiectasis	2.1
Arrhythmia	2.1
Neuralgia, Neuritis, Neuropathy	2.1
Eps, Potential Eps, Tardive Dyskinesia	2.1
Cramps, Muscle Spasm	2.1

Reviewer created table from the Study 6002-018 ADAE dataset with TRTEMFL=Y, SAFFL=Y grouped by USUBJID, AEDECOD, and TRTA.

In Pool 8, the incidence of a subject reporting at least one TEAE was 68.7% (504/734) and was similar to Pool 1.

The following table lists TEAEs (and groupings of closely related TEAEs using the ODE-1 methodology) in Pool 8. Dyskinesia, Dyspepsia/Nausea/Vomiting/Indigestion/Epigastric pain/Gastritis/Duodenitis, and Abdominal Pain/Distention/Bloating/Spasm/IBS occurred in 16%, 7%, and 7%, respectively, of istradefylline-treated subjects.

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Table 25. Treatment-Emergent Adverse Events with an Incidence of At Least 2% and at Least 1% Greater than Placebo Occurring in Pool 8, Grouped.

Treatment-emergent Adverse Events, grouped	IST 20 mg N=356 %	IST 40 mg N=378 %	All IST N=734 %	Placebo N=426 %
Dyskinesia	14.6	16.7	15.7	7.5
Dyspepsia, Nausea, Vomiting, Indigestion, Epigastric Pain, Gastritis, Duodenitis	6.2	8.2	7.2	5.9
Abdominal Pain, Distension, Bloating, Spasm, IBS	6.5	7.1	6.8	4.5
Nausea, Vomiting	4.8	6.9	5.9	4.7
Constipation	5.3	5.6	5.4	2.8
Insomnia, Sleep Disturbance, Abnormal Dreams	2.2	7.9	5.2	4.7
Dizziness, Light-headedness	3.1	5.6	4.4	3.8
Psychosis, Delusions, Hallucinations	2.2	6.1	4.2	2.6
Somnolence, Fatigue, Sedation	5.3	2.4	3.8	3.8
Confusion, Delirium, Altered Mental Status, Disorientation, Coma	4.8	2.4	3.5	3.5
Insomnia	0.6	6.1	3.4	3.5
Diabetes, Glucose Intolerance, Hyperglycemia, HbA1c, Glycosuria, Ketones	2.2	2.9	2.6	0.7
Bleeding	3.4	1.6	2.5	2.1
Anxiety, Nervousness, Panic attacks	2.2	2.4	2.3	1.4
Hematuria	3.1	1.6	2.3	1.4
Anorexia, Decreased appetite	1.1	2.9	2	1.2
Weight loss, Catabolic State, Cachexia, Failure To Thrive	2.2	1.3	1.8	1.2

Treatment-emergent Adverse Events, grouped	IST 20 mg N=356 %	IST 40 mg N=378 %	All IST N=734 %	Placebo N=426 %
Fracture	2.8	0.8	1.8	1.6
Dermatitis	0.6	2.4	1.5	0.7
Elevated BUN or Cr, Anuria, ARF, CRF, Oliguria	0.8	2.1	1.5	0.2
Weight Gain	2.5	0.5	1.5	1.9

Reviewer created table from the ISS ADAE dataset with TRTEMFL=Y, ANL01FL=Y, studyID=6002-US-005, 6002-0608, 6002-009, 6002-US-013. Grouped by USUBJID, AEDECOD, and TRPO1A.

The following table lists TEAEs by preferred term in Pool 8. Dyskinesia, Constipation, and Nausea occurred in 16%, 5%, and 5%, respectively, of istradefylline-treated subjects.

Table 26. Treatment-Emergent Adverse Events with an Incidence of At Least 2% and Greater than Placebo Occurring in Pool 8.

Treatment-emergent Adverse Events (preferred term)	IST 20 mg N=356 %	IST 40 mg N=378 %	All IST N=734 %	Placebo N=426 %
Dyskinesia	15	17	16	8
Constipation	5	6	5	3
Nausea	4	6	5	5
Dizziness	3	6	4	4
Hallucination[1]	2	6	4	3
Insomnia	1	6	3	4
Decreased Appetite	1	3	2	1
Diarrhoea	1	2	2	1
Upper Respiratory Tract Inflammation	1	2	2	0
Blood Glucose Increased	1	2	2	0
Protein Urine Present	1	2	2	1
Blood Alkaline Phosphatase Increased	1	2	2	1
Blood Urea Increased	1	2	1	0
Dermatitis Contact	1	2	1	1
Rash	1	2	1	1

Reviewer created table from the ISS ADAE dataset with TRTEMFL=Y, ANL01FL=Y, studyID=6002-US-005, 6002-0608,

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6002-009, 6002-US-013. Grouped by USUBJID, AEDECOD, and TRPO1A. 1 =Includes Preferred Terms Hallucinations, Hallucinations Visual, Hallucinations Olfactory, Hallucinations Somatic, Hallucinations Auditory.

For a review of the laboratory values of blood urea and urine protein, the reader is referred to the Laboratory Findings section of this review.

I searched for terms related to abnormal thinking and behavior in Pools 1 and 8. I included the following preferred terms in my search: Paranoia; Delusion; Hallucination; Auditory Hallucination; Olfactory Hallucination; Visual Hallucination; Mixed Hallucinations; Somatic Hallucination; Confusional State, Mania, Disorientation, Aggression, Agitation, and Delirium.

Abnormal behavior occurred at a higher incidence in istradefylline-treated subjects compared to placebo-treated subjects in Pool 1 (5.7% in the 40 mg dose arm versus 2.8%, respectively).

I searched Pool 4 for the preferred term of dyskinesias as istradefylline was used as monotherapy in this pool. Dyskinesias were reported in one subject (0.3%) in the 40 mg dose group.

Table 27. Incidence of a Subject Experiencing At Least One Treatment-Emergent Adverse Events Related to Abnormal Behavior in Pool 1.

IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
5.9	3.9	5.7	9.7	5.3	2.8

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A.

The following preferred terms occurred in istradefylline-treated subjects in Pool 1: Paranoia; Delusion; Hallucination; Auditory Hallucination; Olfactory Hallucination; Visual Hallucination; Mixed Hallucinations; Somatic Hallucination; Confusional State, Mania, Disorientation, Agitation, and Delirium.

Pool 8 had similar findings to Pool 1 in that a higher incidence of abnormal behavior was noted in istradefylline-treated subjects compared to placebo-treated subjects (6.1% in 40 mg dose arm versus 2.8% in placebo).

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Table 28. Incidence of a Subject Experiencing At Least One Treatment-Emergent Adverse Events Related to Abnormal Behavior in Pool 8.

IST 20 mg N=356 %	IST 40 mg N=378 %	All IST N=734 %	Placebo N=426 %
2.5	6.1	4.4	2.8

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, studyID=6002-US-005, 6002-0608, 6002-009, 6002-US-013. Grouped by USUBJID and TRPO1A.

The following preferred terms occurred in istradefylline-treated subjects in Pool 8: Delusion; Hallucination; Auditory Hallucination; Olfactory Hallucination; Visual Hallucination; Mixed Hallucinations; Somatic Hallucination; Confusional State, Mania, Agitation, and Delirium.

I searched for terms related to abnormal thinking and behavior excluding terms related to hallucinations in Pool 8. I included the following preferred terms in my search: Paranoia; Delusion; Abnormal behavior; Persecutory Delusion; Confusional State, Mania, Disorientation, Aggression, Agitation, and Delirium. The following table shows incidence of abnormal behavior in Pool 8 with these search terms.

Table 29. Incidence of a Subject Experiencing At Least One Treatment-Emergent Adverse Events Related to Abnormal Behavior excluding Hallucinations in Pool 8.

IST 20 mg N=356 %	IST 40 mg N=378 %	All IST N=734 %	Placebo N=426 %
0.6	1.6	1.1	0.9

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, studyID=6002-US-005, 6002-0608, 6002-009, 6002-US-013. Grouped by USUBJID and TRPO1A.

In summary, the most common TEAEs reported in Pool 1 were Dyskinesias, Fall/Dizziness/Balance Disorder/Gait Disturbance/Difficulty Walking, and Dyspepsia/Nausea/Vomiting/Indigestion/Epigastric Pain/Gastritis/Duodenitis. These TEAEs were similar to the most common TEAEs occurring in Pool 1 of the original submission and similar to Pool 8.

8.4.1. Laboratory Findings

The sponsor did not identify a safety signal with laboratory findings in Pool 1 or Pool 2.

The sponsor analyzed laboratory values mean change from baseline to endpoint, shift analyses, and potentially clinically significant (PCS) values in the controlled clinical trials. I found the sponsor's analysis of laboratory findings to be adequate.

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I did not find any clinically significant differences in mean change from baseline for chemistry, hematology or urine analysis values in Pools 1 and 2 because of the small magnitude of change seen in values. This was similar to Dr. Podskalny's review of mean changes in labs in the original submission. For Pools S1 and S2, I did not find any clinically significant differences in mean change from baseline for chemistry and hematology values because of the small magnitude of change seen in values.

The sponsor performed an analysis of shifts to high and low parameters between placebo and istradefylline-treated subjects in Pools 1 and 2 for hematology, chemistry, and urine analysis parameters.

The following table shows normal to high shifts in laboratory parameters in Pool 1. The following laboratory parameters had shifts from normal to high for all istradefylline-doses combined with incidence of at least greater than 2% above placebo: blood urea nitrogen (BUN), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), Glucose, Urate, Creatine Kinase. For all istradefylline doses combined, the difference in incidence from placebo for any laboratory analyte was no higher than 3%. Dr. Podskalny's review of the original submission notes increases in AST and ALT in a dose-related pattern in Pool 1. This submission shows an increase in AST for the 20 mg, 40 mg, and 60 mg dose at 6%, 8%, and 14% compared to placebo of 5%, respectively. Increases in ALT were also noted for the 20 mg, 40 mg, and 60 mg dose at 4%, 6%, and 10% compared to placebo of 5%, respectively.

Table 30. Normal to High Shifts in Laboratory Parameters with Incidence of at Least 2% Greater than Placebo Occurring in Pool 1.

Analyte	IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
BUN	14	22	19	16	19	17
AST	6	6	8	14	7	5
LDH	8	11	12	10	11	8
Glucose	20	18	20	26	20	17
Urate	3	6	6	0	6	3
Creatine Kinase	20	20	20	18	20	18

The data in this table was taken from Table 7.1.2-1 from the ISS.

In Pool S1 for shifts from normal to high and normal to low parameters, the following laboratory values had normal to high shifts in values with an incidence of at least 2% above placebo for all istradefylline doses combined: BUN, AST, LDH, glucose, and urate. No incidence

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was greater than 4% above placebo. Istradefylline-treated subjects compared to placebo-treated subjects had higher incidence of normal to low shifts for eosinophils.

Table 31. Normal to High and Normal to Low Shifts in Laboratory Parameters with Incidence of at Least 2% Greater than Placebo Occurring in Pool S1.

Analyte	IST 20 mg N=442 %	IST 40 mg N=456 %	All IST N=898 %	Placebo N=449 %
Normal to Low Shifts				
Eosinophils	4	4	4	2
Normal to High Shifts				
BUN	26	25	26	21
AST	7	6	7	4
LDH	14	14	14	10
Glucose	17	20	19	17
Urate	6	9	7	3

The data in this table was taken from Table 7.2.2-2 from the ISS.

In Pool S2, the following laboratory values had shifts in values with an incidence of at least 2% above placebo for all istradefylline doses combined: decrease in leukocytes, monocytes, eosinophils and calcium; increase in BUN, AST, alkaline phosphatase (ALK PHOS), LDH, glucose, cholesterol and creatine kinase. No incidence was greater than 4% above placebo except for an increase in BUN which had a difference of 9% above placebo.

Table 32. Normal to High and Normal to Low Shifts in Laboratory Parameters with Incidence of at Least 2% Greater than Placebo Occurring in Pool S2.

Analyte	IST 20 mg N=241 %	IST 40 mg N=249 %	All IST N=490 %	Placebo N=245 %
Normal to Low Shifts				
Leukocytes	10	9	10	7
Monocytes	3	4	4	<1
Eosinophils	7	8	8	4
Calcium	6	4	5	3
Normal to High Shifts				
BUN	31	28	30	21
AST	9	7	8	4
ALK PHOS	10	10	10	8
LDH	15	14	14	11

Analyte	IST 20 mg N=241 %	IST 40 mg N=249 %	All IST N=490 %	Placebo N=245 %
Glucose	24	31	28	24
Cholesterol	13	18	16	13
Creatine Kinase	21	20	21	19

The data in this table was taken from Table 7.2.2-3 from the ISS.

I reviewed the sponsor's analysis of potentially clinically significant (PCS) values and did not find an imbalance between istradefylline and placebo in Pools 1, S1, and S2 for chemistry or hematology parameters (difference ≤ 2%).

I note that the sponsor's analysis of PCS values in Pool 2 showed that 8% of subjects had a glucose level of ≥ 1.5 the upper limit of normal (highest ULN in the current submission of 120 mg/dL). This is a higher incidence than reported in the original submission of 1.7%; however, this may in part be due to differences in definition of potentially clinically significant values between the submissions. The original submission had a PCS glucose level defined as > 250 mg/dL.

There were no TEAEs occurring in subjects who received istradefylline belonging to the SOC Investigations with incidence ≥ 2% above placebo in Pool 1.

The following table shows TEAEs belonging to the SOC Investigations with incidence of at least 2% in any istradefylline group for Pool 2. No incidence was higher than 5%. Differences in incidences seen in the 20 mg group compared to the 40 mg and 60 mg groups may in part be explained by the smaller number of subjects within that dose group as well as by a difference in race as the 20 mg group was comprised of 100% Asians.

Table 33. TEAEs Belonging to SOC Investigations with an Incidence of At Least 2% Occurring in Pool 2.

MedDRA System Organ Class (preferred term)	IST 20 mg N=60 %	IST 40 mg N=1501 %	IST 60 mg N=332 %	All IST N=1893 %
Blood Creatine Phosphokinase Increased	0	4.3	2.7	3.9
Lipase Increased	5	1.6	3.6	2.1
Amylase Increased	3.3	0.8	3.3	1.3
Blood Glucose Increased	5	1.3	0.6	1.3
Aspartate Aminotransferase Increased	3.3	0.7	0.9	0.8
Alanine Aminotransferase Increased	3.3	0.7	0.3	0.7

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MedDRA System Organ Class (preferred term)	IST 20 mg N=60 %	IST 40 mg N=1501 %	IST 60 mg N=332 %	All IST N=1893 %
Blood Trypsin Increased	5	0.3	0	0.4
Gamma-Glutamyl transferase Increased	5	0.2	0	0.3

Reviewer created table from the ISS ADAE dataset with SAFPO2FL=Y, ANLO2FL=Y, SOC= Investigations grouped by USUBJID, AEDECOD, and TRPO2A.

Using the MAED tool, I searched for TEAEs related to laboratory analysis belonging to narrow SMQs with incidence of at least 1% greater than placebo for Pool 1. The only TEAEs related to laboratory analysis belonged narrow SMQ with incidence of at least 1% greater than placebo was Hyperglycaemia/New Onset Diabetes Mellitus. The following table shows the incidence by dose. Overall, the maximum difference from placebo was low at < 2%.

Table 34. TEAEs Belonging to the Narrow SMQ Related to Laboratory Investigation with an Incidence of at Least 1% Greater Than Placebo Occurring in Pool 1.

SMQ term	IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	Placebo N=1010 %
Hyperglycaemia/new onset diabetes mellitus	0.7	1.5	1.7	1.3	0.5

The reviewer created table using the MAED tool and ISS ADAE dataset with SAFP1FL=Y, ANLO1FL=Y.

Laboratory Parameters Related to Elevated Liver Enzymes

The sponsor searched for TEAEs related to increased liver enzymes and did not find a safety signal in istradefylline treated subjects.

The sponsor searched for TEAEs with the following preferred terms: Aspartate Aminotransferase Increase; Blood Bilirubin Increased; Alanine Aminotransferase Increased; Hepatic Enzyme Increased; Gamma-Glutamyl transferase Increased; Liver Function Test Abnormal; Transaminases Increased; Hyperbilirubinemia; Hepatic Function Abnormal; Liver Disorder; Urobilinogen Urine Increased; Urine Bilirubin Increased. Subjects who received istradefylline had similar incidence of reporting any TEAE related to increased liver enzymes compared to subjects who received placebo (1.8% versus 2.0%, respectively). A similar search in Pools S1 and S2 did not show a higher incidence of increased liver enzymes in istradefylline-treated subjects compared to placebo-treated subjects. In Pool 1, fewer than 1% of patients had ALT or AST greater than 3X ULN or 5X ULN. Only 1 patient (20 mg istradefylline) had AST greater than 10X ULN and no patient had ALT greater than 10 X ULN. In Pool 2 fewer than 1% of patients had treatment emergent ALT or AST greater than 3X, 5X, or 10X ULN.

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I did not identify any Hy's law cases in Pools 1, 2 or Study 6002-018. The sponsor notes a case ([(b) (6)]) from study 6002-INT-001 of a 70 year-old man with history of Gilbert's disease (baseline bilirubin elevation of 1.4 mg/dL with the ULN being 1.2 mg/dL) who had elevation of bilirubin to 2.8 mg/dL and AST to 133 U/L (ULN 36 U/L) at Week 8. Istradefylline was not stopped and by Week 12 his AST had returned to normal and his bilirubin to baseline. His history of Gilbert's disease was thought to be a contributory factor for his liver function test elevation and the case was not thought to be treatment related.

There was one case of drug-induced liver injury from study 6002-018 (Subject 6002-[(b) (6)]) which occurred in the setting of istradefylline use and paracetamol use and is summarized in the section on deaths.

Blood Urea Nitrogen

I evaluated blood urea nitrogen as subjects who received istradefylline 40 mg in Pool 8 were noted to have a higher incidence of the TEAE of Urea Nitrogen Increase compared to subjects who received placebo (2% versus 0%, respectively). I note that more istradefylline-treated subjects had shifts to high values compared to placebo-treated subjects in Pool 1.

A higher incidence in normal to high shifts for urea nitrogen was seen in istradefylline-treated subjects compared to placebo-treated subjects (19% versus 17%, respectively). The following table shows normal to high shifts at any visit for urea nitrogen for Pool 1.

Table 35. Percentage of Normal to High Shifts at Any Visit for Urea Nitrogen for Pool 1

IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
14	22	19	16	19	17

The above data was taken from the ISS Table 7.2.2-1.

No dose-response was noted in Pool 1 for subjects reporting the TEAE of increased blood urea. The following table shows incidence of the TEAE of Blood Urea Increased in Pool 1.

Table 36. Treatment-Emergent Adverse Events of Blood Urea Increased Present Occurring in Pool 1.

IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
0.7	0.7	1.3	1.3	1	0.5

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped by USUBJID, AEDECOD, and TRPO1A.

No difference was noted in mean change from baseline to endpoint for urea nitrogen. The following table shows mean change from baseline to endpoint for urea nitrogen for Pool 1.

Table 37. Mean change from Baseline to Endpoint for Urea Nitrogen for Pool 1

Laboratory Parameters	IST 10 mg N=153	IST 20 mg N=869	IST 40 mg N=896	IST 60 mg N=155	Placebo N=1010
Urea Nitrogen (mmol/L)	0.2	0.2	0.1	0.2	0.1

The above data was taken from the ISS Table 7.2.1-1.

Istradefylline-treated groups did not have a higher incidence in potentially clinically significant values for urea nitrogen compared to the placebo-treated group in Pool 1.

In summary, a higher incidence of istradefylline-treated subjects in Pool 8 reported the TEAE of Urea Nitrogen Increased compared to placebo-treated subjects. Additionally, a higher incidence of normal to high shifts for urea nitrogen were noted in istradefylline-treated subjects compared to placebo-treated subjects (19% versus 17%, respectively) in Pool 1 although there was no dose response from 20 to 60 mg.

Urine Protein

I evaluated urine protein as subjects who received istradefylline 40 mg in Pool 8 were noted to have a higher incidence of the TEAE of Protein Urine Present compared to placebo-treated subjects (2% versus 1%, respectively). I did not find a higher incidence of TEAEs reported in Pool 1 in istradefylline-treated subjects. Istradefylline-treated subjects had similar incidences of urine protein present in Pool 1 compared to placebo-treated subjects.

Subjects who received istradefylline had a similar incidence of reporting the TEAE of Protein Urine Present compared to subjects who received placebo in Pool 1 (0.5% versus 0.6%, respectively). The following table shows incidence of the TEAE of Protein Urine Present in Pool 1.

Table 38. Treatment-Emergent Adverse Events of Protein Urine Present Occurring in Pool 1.

IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
0	0.3	0.9	0	0.5	0.6

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped by USUBJID, AEDECOD, and TRPO1A.

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Istradefylline-treated groups did not have higher than 1% difference in incidence of urine protein in Pool 1 compared to the placebo-treated group in Pool 1 at any timepoint from Baseline to Endpoint.

In summary, no increased incidence of urine protein was noted with TEAEs reported in Pool 1 or by an analysis of urine protein in Pool 1.

Overall for the laboratory findings section of the review, I note a higher incidence of urea nitrogen increased in istradefylline-treated subjects compared to placebo.

8.4.2. Vital Signs

In Pools 1, S1 and S2, small increases in systolic blood pressure were noted to occur in istradefylline-treated subjects. In Pools S1 and S2, a higher incidence of istradefylline-treated subjects had decreases in body weight compared to placebo-treated subjects.

In terms of methods for analyzing vital signs, the sponsor analyzed mean change from Baseline to Endpoint for vital signs and PCS values for Pools 1, 2, S1, and S2. Additionally, the sponsor provided an analysis for orthostatic hypotension for Pools S1 and S2. I found the sponsor's review method to be adequate.

In Pool 1, the 60 mg dose showed an increase in mean sitting blood pressure of 1.9 mmHg from baseline, whereas placebo showed a mean decrease of -1.6 mm Hg. No clinically meaningful mean change was noted with sitting systolic blood pressure with the 10 mg, 20 mg, and 40 mg doses because of the small magnitude of change seen (< 1 mmHg). The following table shows mean change in systolic blood pressure values for all doses from Baseline to Endpoint for Pool 1.

Table 39. Mean Change from Baseline to Endpoint for Sitting Systolic Blood Pressure (mmHg) for Pool 1.

IST 10 mg n=153	IST 20 mg n=869	IST 40 mg n=896	IST 60 mg n=155	PBO n=1010
0.8	0.1	-0.2	1.9	-1.6

The data in this table was taken from the Table 8.1.1-1 from the ISS.

In Pool S1, a small increase in mean systolic blood pressure was noted in subjects who received istradefylline 40 mg whereas a mean decrease was noted for placebo. Pool S2 showed similar findings of the same magnitude.

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Table 40. Mean Change from Baseline to Endpoint for Sitting Systolic Blood Pressure (mmHg) for Pool S1.

IST 20 mg n=442	IST 40 mg n=456	PBO n=449
-1.7	0.3	-2.0

The data in this table was taken from the Table 8.1.1-2 from the ISS.

Table 411. Mean Change from Baseline to Endpoint for Sitting Systolic Blood Pressure (mmHg) for Pool S2.

IST 20 mg n=241	IST 40 mg n=249	PBO n=245
-1.7	0.3	-2.0

The data in this table was taken from the Table 8.1.1-3 from the ISS.

Pool 8 similarly showed a very small mean change in blood pressure for istradefylline.

Table 422. Mean Change from Baseline to Endpoint for Sitting Systolic Blood Pressure (mmHg) for Pool 8.

IST 20 mg n=356	IST 40 mg n=378	PBO n=426
0.0	0.3	-1.2

Data is taken from the 08/08/2019 response to an information request dated 07/08/2019.

No imbalance in PCS changes with sitting blood pressure were seen for Pools 1, S1, or S2 in istradefylline-treated subjects compared to placebo (difference less than 1%).

Low weight (defined as decrease of ≥7% relative to baseline) was noted to occur at higher frequency in istradefylline-treated subjects compared to placebo-treated subjects in Pool S1 (4.2% vs 2.2%). Pool S2 showed similar findings of increased incidence of low weight in istradefylline-treated subjects. Mean body weights were similar between Baseline and Endpoint in istradefylline-treated subjects in Pools 1, S1, and S2.

No clinically meaningful changes were noted for diastolic blood pressure, pulse rate, and respiratory rate from Baseline to Endpoint in Pools 1, S1, and S2.

In Pool 2, body weight decreased by a mean of 1.7 kg from baseline to endpoint. A review of PCS values for Pool 2 showed a higher incidence of subjects with low weight compared to high weight (24.7% vs 9.2%, respectively). The higher incidence of low weight compared to high weight in Pool 2 may be due in part to the natural history of Parkinson's disease.

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In Pool 2, blood pressure, pulse rate, respiratory rate, did not have a clinically meaningful difference (small magnitude of change) between baseline and endpoint values. There was a low incidence of subjects with PCS values for blood pressure and pulse rate (less than 5%).

Per Dr. Podskalny's review of the original submission, orthostatic vital signs were assessed Study 6002-US-006 and no evidence of orthostasis was seen. No increased incidence of orthostasis (defined as systolic blood pressure decrease of ≥20 mmHg, diastolic blood pressure decrease of ≥10 mmHg) at endpoint was seen in istradefylline- compared to placebo-treated subjects in Pools S1 or S2.

I searched for TEAEs belonging to the SMQs related to vital signs in Pool 1 and did not find any TEAEs occurring in istradefylline-treated subjects with incidence greater than 2% above placebo-treated subjects.

In summary, no signal was observed for increases in systolic blood pressure in istradefylline-treated subjects in Pools 1, S1 and S2. No imbalance in PCS changes in blood pressure were noted in Pools 1, S1, and S2 between istradefylline and placebo. Low weight occurred more frequently in istradefylline-treated subjects in Pools S1 and S2; however, mean body weights were similar between Baseline and Endpoint in Pools 1, S2, and S2. No imbalance was seen in orthostasis occurring in istradefylline- compared to placebo-treated subjects in Pools S1 and S2.

8.4.3. Electrocardiograms (ECGs)

The sponsor performed an analysis of ECG-related changes and adverse events and did not find any evidence of increased incidence in istradefylline-treated subjects.

The sponsor performed an analysis of mean change from baseline to endpoint for ECG parameters. No clinically meaningful changes were noted in Pool 1 due to small magnitudes of change seen.

Subjects who received istradefylline had similar incidences of clinically significant abnormal ECG interpretations compared to subjects who received placebo in Pools 1, S1, and S2 (difference < 2.0%).

Subjects who received istradefylline had similar incidences of treatment-emergent PCS ECG values at any visit in Pool 1 compared to subjects who received placebo (difference < 2.1%).

Subjects who received istradefylline had similar incidences of treatment-emergent shifts in ECG Values from Normal to PCS at any visit in Pool 1 compared to subjects who received placebo (difference < 1.5%).

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In Pool 2, no clinically meaningful changes were noted in mean change from baseline to endpoint for ECG parameters for Pool 2 due to small magnitudes of change seen.

The incidence of subjects with clinically significant abnormal ECG was less than 2.0% at visits occurring from Baseline through Endpoint in Pool 2.

The incidence of subjects with any treatment-emergent PCS ECG values at any visit was less than 7% in Pool 2. The higher incidence may be due to the longer duration of the studies in Pool 2 compared to Pool 1.

The incidence of subjects with treatment-emergent shifts in ECG values from Normal to PCS at any visit was less than 2.5% in Pool 2.

I searched for TEAEs belonging to the narrow SMQs related to ECG changes in Pool 1 and did not find any TEAEs occurring in istradefylline-treated subjects with incidence greater than 2% above placebo-treated subjects.

In summary, no safety signal was identified related to ECG changes in Pools 1, S1, S2, or 2.

8.4.4. QT

A thorough QT study (study 6002-US-024) was performed in healthy subjects who received 40 mg and 160 mg doses of istradefylline and reviewed in the original submission. Per Dr. Podskalny's review, the QT team found that istradefylline did not affect the QTc duration to a clinically significant degree.

8.4.5. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Impulse Control Disorder

The sponsor did not find increased incidence of TEAEs related to impulse control disorder or evidence of impulse control disorder using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) occurring in istradefylline-treated subjects.

The sponsor searched for TEAEs with the following preferred terms: Impulse-Control Disorder; Libido Increased; Gambling Disorder; Hypersexuality; Obsessive-Compulsive Disorder; Disturbance in Sexual Arousal. In Pool 1, thirteen istradefylline-treated subjects reported TEAEs related to impulse control disorder compared to no cases in placebo-controlled subjects. The

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incidence of impulse control disorder was 0% in the placebo group and 0.7%, 0.8%, 0.6%, and 0% in the istradefylline 10, 20, 40 and 60 mg/day groups, respectively, in Pool 1.

No increased incidence of TEAEs related to impulse control disorder were noted in istradefylline-treated subjects in Pools S1 or S2. None of the TEAEs related to impulse control disorder were serious.

Impulse control disorder was reported in one subject treated with 40 mg dose in Pool 8, compared to no subjects treated with the 20 mg dose or placebo.

Postmarketing data showed two adverse drug reactions of impulse control disorder. The first case occurred in a man in his 80s who had impulse control disorder develop one week after istradefylline use. His symptoms resolved with cessation of istradefylline. The second case occurred in a 74-year-old man who developed impulse control disorder and attempted suicide within 10 days of starting therapy. Concomitant medications that were potential confounders in the case included rotigotine, carbidopa monohydrate, and levodopa.

Reviewer comment: Levodopa/carbidopa is associated with risk for impulse control disorder and therefore is a potential confounding factor in cases of impulse control disorder occurring in Pool 1, where subjects used istradefylline as adjunctive treatment for Parkinson's disease. I searched for TEAEs related to impulse control disorder in Study 6002-EUO4 (from Pool 3) and studies from Pool 4 as subjects used istradefylline as monotherapy in these studies. I did not find any TEAEs related to impulse control disorder. The absence of TEAEs related to impulse control disorder in Study 6002-EU04 and Pool 4 and presence in Pool 1 suggest that these TEAEs maybe related to concomitant medication use with levodopa/carbidopa or levodopa/benserazide. The first postmarketing case of impulse control disorder that occurred within one week of istradefylline use and resolved after cessation of istradefylline suggests a possible causal association given the timing of onset of symptoms to initiation of drug and resolutions of symptoms with cessation of drug. A role for istradefylline in the second postmarketing case in the 74-year-old man cannot be ruled out given that symptoms occurred within 10 days of initiation of istradefylline however confounding factors exist including concomitant medication use with rotigotine, carbidopa monohydrate, and levodopa.

The QUIP-RS was used in Study 6002-014 to assess for thoughts, urges/desires, and behaviors associated with impulse control disorders (compulsive gambling, buying, eating, and sexual behavior) and disorders of medication use and hobbyism/punding. Higher scores indicate more severe symptoms and the maximum value on the scale is 112. QUIP-RS scores were collected at baseline, Week 6, and Week 12.

Mean QUIP-RS scores were not higher at Week 6 or Week 12 compared to baseline values in istradefylline-treated subjects. At Week 12, subjects who received istradefylline 20 mg had a

mean decrease of 1.6 points from baseline and subjects who received istradefylline 40 mg had a mean decrease of 1.4 points.

In summary, istradefylline-treated subjects had similar incidence of TEAEs related to impulse control disorder compared to placebo-controlled subjects in Pool 1 (difference < 1 %); however, all cases of impulse control disorder (13 cases) occurred in istradefylline-treated subjects, compared to no cases in placebo-treated subjects. No subjects in Study 6002-EU-4 or Pool 4 reported TEAEs related to impulse control disorder. Endpoint QUIP-RS scores were not higher than baseline scores in a 12-week study in istradefylline-treated subjects. Two postmarketing cases of impulse control disorder occurred within 10 days of initiation with istradefylline and one of the cases had resolution of symptoms with cessation of istradefylline. Overall, these findings suggest that istradefylline may be associated with impulse control disorder.

8.5.2. Dizziness, Hypotension, Orthostatic Hypotension

The sponsor searched for TEAEs related to dizziness, hypotension, and orthostatic hypotension in Pool 1 and noted an increase in the incidence of dizziness occurring in istradefylline-treated subjects.

The sponsor searched for TEAEs with the following preferred terms: Dizziness; Orthostatic Hypotension; Vertigo; Dizziness Postural; Hypotension; Blood Pressure Decreased; Vertigo Positional; Procedural Hypotension. Subjects who received istradefylline more frequently reported any TEAE related to dizziness, hypotension, or orthostatic hypotension compared to subjects who received placebo; however, the difference was small (2.8%). The top three preferred terms that made up this grouping included dizziness, orthostatic hypotension, and vertigo, and the following table shows incidence of these TEAEs by dose. There is no evidence of a dose-response for the TEAE of orthostatic hypotension or vertigo for Pool 1.

Table 43. Incidence of top 3 TEAEs Related to Dizziness, Hypotension or Orthostatic Hypotension by Dose in Pool 1.

MedDRA (Preferred term)	IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
Any TEAE*	9.2	9.4	7.4	16.1	9.0	6.2
Dizziness	5.2	5.1	4.9	14.2	5.7	4.2
Orthostatic Hypotension	1.3	2.2	0.7	0	1.3	1.1
Vertigo	1.3	0.9	1.2	0.6	1.1	0.5

* Any TEAE related to dizziness, hypotension, or orthostatic hypotension. Data for this table was taken from the ISS Table document Table 5.3.5.3.2-2.2.22.1.1.7.

An analysis in Pools S1 and S2 showed findings similar to Pool 1 of small increases (overall difference <2%) in incidence of TEAEs related to the combined terms of dizziness, hypotension,

and orthostatic hypotension among istradefylline-treated subjects compared to placebo-treated subjects. A review of vital signs showed no evidence of orthostatic hypotension in Pools S1 or S2 or hypotension in Pools 1, S1, or S2.

In Pool 8, istradefylline-treated subjects reported a higher incidence of the TEAE of dizziness compared to the placebo group (6% of the 40-mg dose group versus 4%, respectively). Istradefylline-treated subjects did not have a higher incidence of the TEAE Orthostasis compared to placebo-treated subjects (1.5% versus 2.1%, respectively).

In summary, istradefylline-treated subjects were noted to have a higher incidence of dizziness compared to placebo-treated subjects. There was no evidence of orthostasis or hypotension by TEAE reported or by vital sign analysis.

8.5.3. Falls

The sponsor did not find increased incidence of TEAEs related to falls, fractures, or injury in istradefylline-treated subjects.

The sponsor searched for treatment-emergent adverse events related to falls, fractures, and injury in Pool 1. The search included AEs with the following preferred terms: Fall; Contusion; Skin Abrasion; Laceration; Rib Fracture; Ligament Sprain; Spinal Compression; Limb Injury; Hip Fracture; Foot Fracture; Head Injury; Traumatic Haematoma; Eyelid Injury; Haematoma; Humerus Fracture; Pelvic Fracture; Periorbital Haematoma; Acetabulum Fracture, Face Injury; Facial Bone Fracture; Fracture; Ilium Fracture; Joint Injury; Radius Fracture; Sternal Fracture; Forearm Fracture; Hand Fracture; Injection Site Haematoma; Lumbar Vertebral Fracture; Musculoskeletal Injury. Subjects who received istradefylline had similar incidence of reporting a TEAE related to falls, fractures, and injury compared to subjects who received placebo (8.0% versus 7.6%, respectively). Pool S1 had similar findings to Pool 1. Pool S2 had a small increase in incidence of falls occurring in subjects who received istradefylline compared to subjects who received placebo (5.5% versus 4.5%, respectively).

8.5.4. Effects on Ability to Drive

The sponsor did not find a safety signal of increased Road Traffic Accidents with istradefylline using an evaluation of TEAEs.

The sponsor performed a search for TEAEs of Road Traffic Accident occurring in Pool 1. The TEAE of Road Traffic Accident occurred in one subject who received istradefylline 20 mg, four subjects who received istradefylline 40 mg, and one subject who received placebo. The incidence of Road Traffic Accident was similar between istradefylline-treated subjects compared to placebo-treated subjects (0.2% versus 0.1%, respectively). The sponsor notes that it is not known if any of the subjects were operating the vehicle at the time of the accident. One

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subject experienced loss of consciousness; however, it is not known if it occurred before or after the accident.

I note two TEAEs of Road Traffic Accident in Pool 2, both occurring in the 40 mg dose (incidence of 0.1% (2/1893)). In study 6002-018, there was one TEAE of Road Traffic Accident (incidence of 0.4% (1/239).

The low number of TEAEs of Road Traffic Accident does not suggest an increased risk for road traffic accidents with istradefylline.

8.5.5. Cardiac Safety

The sponsor assessed cardiac safety, as treatment-related serious TEAEs belonging to the Cardiac SOC were noted to occur. The sponsor did not identify a safety signal for cardiac safety.

The incidence of treatment-emergent SAEs belonging to the Cardiac Disorder SOC was 0.7% in istradefylline-treated subjects compared to 0.8% in placebo-treated subjects. No dose response was seen.

The incidence of TEAEs belonging to the Cardiac Disorder SOC was 3.0% in istradefylline-treated subjects compared to 3.5% in placebo-treated subjects. The following table shows the incidence of TEAEs by dose.

Table 444. Incidence of A Subject Experiencing at Least One TEAE Belonging to the Cardiac SOC by Dose in Pool 1.

IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
2	3	2.8	5.2	3	3.5

Reviewer created table from the ISS ADAE dataset with TRTEMFL=Y, ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID AESOC=cardiac and TRP01A.

No TEAEs belonging to the Cardiac SOC by preferred term had incidence of at least 1% greater than placebo.

The sponsor did not identify any safety signal from postmarketing adverse events belonging to the Cardiac SOC.

I did not identify a safety signal when I searched for TEAEs with potential ischemic etiology. The following preferred terms were included in my search: Acute Kidney Injury; Angina Pectoris; Angina Unstable; Arrhythmia; Arrhythmia Supraventricular; Atrial Fibrillation; Atrial Flutter;

Atrioventricular Block; Atrioventricular Block First Degree; Atrioventricular Block Second Degree; Bradycardia; Bundle Branch Block; Bundle Branch Block Bilateral; Bundle Branch Block Left; Bundle Branch Block Right; Cardiac Disorder; Cardiac Failure Acute; Cardiac Failure Congestive; Cardiac Murmur; Cardiac Valve Disease; Cardiogenic Shock; Cardio-Respiratory Arrest; Cerebral Infarction; Cerebrovascular Accident; Coronary Artery Disease; Coronary Artery Occlusion; Electrocardiogram Abnormal; Electrocardiogram Qt Prolonged; Electrocardiogram St Segment Abnormal; Electrocardiogram St Segment Depression; Electrocardiogram T Wave Abnormal; Electrocardiogram T Wave Inversion; Hypertension; Myocardial Infarction; Sinus Arrhythmia; Sinus Bradycardia; Sinus Node Dysfunction; Sinus Tachycardia; Sudden Death; Tachycardia; Thrombosis Mesenteric Vessel; Transient Ischaemic Attack; Tricuspid Valve Incompetence; Ventricular Extrasystoles; Ventricular Hypertrophy.

The incidence of TEAEs with potential ischemic etiology was not higher in istradefylline-treated subjects compared to placebo-treated subjects (4% versus 5.3%, respectively). No preferred term for any dose had incidence greater than 1% above placebo.

In summary, no cardiac safety signal was identified in a search of TEAEs related to the Cardiac SOC or TEAEs with potential ischemic etiology.

8.5.6. Suicide

The sponsor did not identify a safety signal for suicidal ideation through review of TEAEs occurring in Pools 1 through 4 or by review of incidence of suicidal behavior in Study 6002-014 as measured by the Columbia Suicide Severity Rating Scale (C-SSRS).

The sponsor searched for TEAEs related to suicidal ideation in Pools 1, 2, 3, and 4 using the preferred terms Depression Suicidal, Suicidal Behavior, Suicidal Ideation, Suicide Attempt. Overall, the sponsor's search method appeared to be adequate.

In Pool 1, two TEAEs of suicidal behavior were reported (incidence of 0.1% (2/2073)). One case involved a suicide attempt (6002-US(b) (6), original submission USUBJID (b) (6)) that was described in Dr. Podskalny's review. The subject had been on lithium as a concomitant medication and I did not think the event was treatment-related. The second case is summarized here.

Suicidal Ideation (6002-(b) (6))
64-year old male with history of depressive disorder reported suicidal ideation while taking istradefylline 20 mg daily. The subject reported the TEAEs of Fall, Road Traffic Accident and Excoriation on Study Day 25 and on Study Day 26 reported the TEAEs of impulse control disorder and suicidal ideation both of mild severity. The suicidal ideation was considered resolved after 17 days. The impulse control disorder was considered resolved after 76 days. No

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dose adjustments were made. Concomitant medications included levodopa, benserazide, rotigotine, and tolcapone. The subject had answered no to all questions on the C-SSRS at baseline.

Reviewer comment: A role for istradefylline in the event of suicidal ideation cannot be established as the subject had a history of depressive disorder, which is a known risk factor for suicidal behavior.

In Pool 2, there were 12 TEAEs related to suicidality belonging to the following preferred terms: Depression Suicidal, Suicide Behavior, Suicidal Ideation (n=8), Suicide Attempt (n=2). Ten TEAEs occurred with the 40 mg dose group (incidence of 0.7% (10/1501) and two TEAEs occurred in the 60 mg dose group (incidence of 0.6% (2/332)). Five of the 12 TEAEs were noted as serious. Of the five subjects who had TEAEs, four subjects had a history of mental health disorder. The fifth case ((b) (6)) is summarized below.

Suicidal Ideation (b) (6))
68-year old man with history of Parkinson's disease, myocardial infarction status post coronary artery bypass grafting, hypertension, insomnia, migraines, was hospitalized on Study Day 286 for depression and suicidal ideation reportedly due to concern for leg cramps and leg pain. The event resolved after 8 days and the subject continued on into the study. Concomitant medications included levodopa, peripheral dopa decarboxylase inhibitor, acetylsalicylic acid, atenolol, atorvastatin, gabapentin, isosorbide dinitrate, pantoprazole, ropinirole, and amitriptyline.

Reviewer comment: A role for istradefylline cannot be ruled out, as the event occurred while the subject was on study drug; however, confounding factors in this case exist including association of depression or suicidality with levodopa/carbidopa and amitriptyline.

No TEAEs of suicidal behavior were reported in istradefylline-treated subjects in Pools 3 or 4. I reviewed Study 6002-018 and did not identify any TEAEs related to suicidal behavior.

The sponsor notes three cases of suicidal behavior that were reported in the post-marketing setting. Two of the three cases were suspected as related by the reporter. Of these two cases, the sponsor notes that one case involved a subject who had a confounding factor of having psychiatric symptoms prior to taking istradefylline. The sponsor notes that the second case involved a subject who had the confounding factor of concomitant medication usage with carbidopa, levodopa, and rotigotine which have been associated with depression.

In Study 6002-014, the sponsor used the C-SSRS to assess for suicidal ideation and suicidal behavior. The 20 mg and 40 mg dose groups did not have higher incidence of suicidal behavior or suicidal ideation at study Weeks 2, 6, 10, and 12 compared to baseline.

In summary, I did not identify a safety signal for suicidal behavior based on TEAEs related to suicidal behavior reported in Pools 1 through 4 or by suicidal ideation and behavior in Study 6002-014 as collected by the C-SSRS.

8.5.7. Neutropenia and Neutropenic Sepsis

The sponsor assessed AEs related to neutropenia and neutropenic sepsis given the association of cases with another adenosine A2A receptor antagonist (tozadenant). The sponsor did not identify a safety signal with istradefylline for neutropenia or neutropenic sepsis.

The sponsor searched for TEAEs related to neutropenia in Pools 1 and 2 with the following preferred terms: White Blood Cell Count Decreased; Leukopenia; Neutropenia; Neutrophil Count Decreased. The sponsor's search method appeared adequate.

In Pool 1, the incidence of TEAEs related to neutropenia was similar between istradefylline-compared to placebo-treated subjects (0.5% versus 0.3%, respectively). In Pool 2, the incidence of TEAEs related to neutropenia was 0.5% for istradefylline-dose combined. No TEAEs related to neutropenia were serious.

The sponsor searched for cases of neutropenic sepsis occurring in Pools 1 through 4. The sponsor identified the following preferred terms as related to TEAEs of sepsis: Pneumonia (the sponsor notes that this term was included as it was the only infection associated with outcome of death), Sepsis, Sepsis Syndrome, Septic Shock, Staphylococcal Sepsis, and Urosepsis. The sponsor then identified subjects who had AEs related to neutropenia occurring ≤14 days prior to the TEAEs related to sepsis. AEs related to neutropenia were searched with the following preferred terms: Agranulocytosis; Granulocytopenia; Leukopenia; Neutropenia; Neutrophil Count Decreased; Neutrophil Percentage Decreased; Pancytopenia; White Blood Cell Count Decreased. The sponsor's search method appeared adequate.

The sponsor identified 16 subjects who met the above criteria. None of the subjects had neutropenia reported concurrently as a TEAE with the TEAE of sepsis. Seven of the 16 subjects had neutrophil counts that were normal or above the upper limit of normal. The other nine subjects did not have laboratory results.

In study 6002-018, two subjects reported the TEAE of sepsis. Neither subject reported TEAEs related to neutropenia. Leukocyte and neutrophil counts were not provided in either of the cases.

The sponsor notes that two cases of sepsis occurred in the post-marketing setting. Neither case reported neutropenia.

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In summary, no safety signal for neutropenia or neutropenic sepsis was identified in istradefylline-treated subjects.

8.5.8. Drug-Drug interactions

The reader is referred to the Clinical Pharmacology review.

8.6. Safety Analyses by Demographic Subgroups

I evaluated five of the most frequent six TEAEs (grouped using the ODE-1 methodology) in Pool 1 and 8 by gender, age group, race, and region.

For gender, I note that dyskinesias occurred at a higher incidence in female compared to male istradefylline-treated subjects (22.6% versus 14.5%, respectively). The following table shows the most frequent TEAEs by gender and dose for Pool 1.

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Table 45. Treatment-Emergent Adverse Events, Grouped Occurring by Gender in Pool 1.

Treatment-emergent Adverse Events, grouped	Istradefylline										Placebo	
	10 mg N=50 %	10 mg N=103 %	20 mg N=369 %	20 mg N=500 %	40 mg N=374 %	40 mg N=522 %	60 mg N=49 %	60 mg N=106 %	All N=842 %	All N=1231 %	N=422 %	N=588 %
Sex	F	M	F	M	F	M	F	M	F	M	F	M
Dyskinesia	30	17.5	20.1	13.2	22.7	14.2	32.7	19.8	22.6	14.5	11.4	8.3
Fall, dizziness, balance disorder	22	10.7	11.1	11.2	15	7.7	22.4	19.8	14.1	10.4	10.9	8.5
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	20	7.8	8.7	6.4	10.2	6.7	30.6	19.8	11.3	7.8	8.1	4.9
Insomnia, sleep disturbance, abnormal dreams	8	13.6	6.8	8.8	10.2	7.7	6.1	14.2	8.3	9.2	5	6
Nausea, vomiting	10	5.8	7	6	7.8	5.9	30.6	18.9	8.9	7.1	6.2	3.9
Abdominal pain, distension, bloating, spasm, IBS	10	8.7	7.3	6.8	8	7.5	8.2	4.7	7.8	7.1	5.9	4.8

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A.F: Female, M:Male.

Pool 8 showed similar results as Pool 1 for gender in that there was a higher incidence of dyskinesias in female compared to male istradefylline-treated subjects (19.0% versus 12.3%, respectively). The following table shows the most frequent TEAEs by gender and dose for Pool 8.

Table 46. Treatment-Emergent Adverse Events, Grouped Occurring by Gender in Pool 8.

Treatment-emergent Adverse Events, grouped	Gender*	All IST %	Placebo %
Dyskinesia	Female	19	9.8
	Male	12.3	5.4
Fall, dizziness, balance disorder	Female	7.6	8.8
	Male	8.8	8.6
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	Female	6.2	6.8
	Male	8.2	5
Insomnia, sleep disturbance, abnormal dreams	Female	4.3	4.4
	Male	6	5
Nausea, vomiting	Female	4.6	5.4
	Male	7.1	4.1
Abdominal pain, distension, bloating, spasm, IBS	Female	6.2	4.9
	Male	7.4	4.1

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, studyID=6002-US-005, 6002-0608, 6002-009, 6002-US-013. Grouped by USUBJID, AEDECOD, and TRPO1A. *Denominator: All IST Female: 369; All IST Male: 365; Placebo Female: 205; Placebo Male: 221.

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For age group, I note that Dyskinesias occurred at a higher incidence in istradefylline-treated subjects <75 years of age compared to subjects ≥75 years of age (18.5% versus 12.8%, respectively) in Pool 1. Fall/Dizziness/Balance Disorder occurred at a higher incidence in istradefylline-treated subjects ≥75 years of age compared to subjects <75 years of age (18.2% versus 11.1%). Similar findings of a higher incidence of Fall/Dizziness/Balance Disorder were seen in istradefylline-treated subjects ≥ 65 years of age compared to subjects < 65 years of age. The following tables show the most frequent TEAEs by age group and dose for Pool 1.

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Table 47. Treatment-Emergent Adverse Events, Grouped Occurring by Age Group <65 versus ≥ 65 Years in Pool 1.

Treatment-emergent Adverse Events, grouped	Istradefylline										Placebo	
	10 mg N=78 %	10 mg N=75 %	20 mg N=423 %	20 mg N=446 %	40 mg N=472 %	40 mg N=424 %	60 mg N=73 %	60 mg N=82 %	All N=1046 %	All N=1027 %	N=539 %	N=471 %
Age Group (years)	<65	**≥65**	<65	**≥65**	<65	**≥65**	<65	**≥65**	<65	**≥65**	<65	**≥65**
Dyskinesia	19.2	24	15.6	16.6	18.4	17	24.7	23.2	17.8	17.8	10.6	8.5
Fall, dizziness, balance disorder	20.5	8	8.7	13.5	9.7	11.8	16.4	24.4	10.6	13.2	8.3	10.8
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	10.3	13.3	8	6.7	8.3	8	27.4	19.5	9.7	8.8	6.5	5.9
Insomnia, sleep disturbance, abnormal dreams	12.8	10.7	8	7.8	10.4	6.8	19.2	4.9	10.2	7.4	6.7	4.2
Nausea, vomiting	6.4	8	6.9	6.1	7	6.4	27.4	18.3	8.3	7.3	5.2	4.5
Abdominal pain, distension, bloating, spasm, IBS	6.4	12	6.4	7.6	7.4	8	6.8	4.9	6.9	7.9	5.2	5.3

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A.

Table 48. Treatment-Emergent Adverse Events, Grouped Occurring by Age <75 versus ≥ 75 Years in Pool 1.

Treatment-emergent Adverse Events, grouped	Istradefylline										Placebo	
	10 mg N=140 %	10 mg N=13 %	20 mg N=751 %	20 mg N=118 %	40 mg N=805 %	40 mg N=91 %	60 mg N=135 %	60 mg N=20 %	All N=1831 %	All N=242 %	N=895 %	N=115 %
Age Group (years)	<75	**≥75**	<75	**≥75**	<75	**≥75**	<75	**≥75**	<75	**≥75**	<75	**≥75**
Dyskinesia	21.4	23.1	16.6	12.7	18.5	11	25.2	15	18.5	12.8	10.1	6.1

Treatment-emergent Adverse Events, grouped	Istradefylline										Placebo	
	10 mg N=140 %	10 mg N=13 %	20 mg N=751 %	20 mg N=118 %	40 mg N=805 %	40 mg N=91 %	60 mg N=135 %	60 mg N=20 %	All N=1831 %	All N=242 %	N=895 %	N=115 %
Age Group (years)	<75	**≥75**	<75	**≥75**	<75	**≥75**	<75	**≥75**	<75	**≥75**	<75	**≥75**
Fall, dizziness, balance disorder	15	7.7	9.7	20.3	10.2	15.4	20	25	11.1	18.2	9.2	12.2
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	11.4	15.4	7.5	6.8	8	9.9	23.7	20	9.2	9.5	5.7	10.4
Insomnia, sleep disturbance, abnormal dreams	12.1	7.7	8	7.6	8.8	7.7	11.9	10	9	7.9	5.6	5.2
Nausea, vomiting	7.1	7.7	6.4	6.8	6.6	7.7	23	20	7.8	8.3	4.7	6.1
Abdominal pain, distension, bloating, spasm, IBS	9.3	7.7	6.7	9.3	7.5	9.9	5.9	5	7.2	9.1	4.8	8.7

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A.

Pool 8 showed similar results as Pool 1 for age group in that dyskinesias occurred more frequently in istradefylline-treated subjects <75 years of age compared to subjects ≥75 years of age. The following tables show the most frequent TEAEs by age group and dose for Pool 8.

Table 49. Treatment-Emergent Adverse Events, Grouped Occurring by Age Group <65 versus ≥ 65 Years in Pool 8.

Treatment-emergent Adverse Events, grouped	Age Group (years)*	All IST %	Placebo %
Dyskinesia	< 65	17.9	7.6
	>= 65	13.7	7.4
Fall, dizziness, balance disorder	< 65	8.1	7.6
	>= 65	8.2	9.8
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	< 65	9.2	6.2
	>= 65	5.4	5.6
Insomnia, sleep disturbance, abnormal dreams	< 65	6.6	6.2
	>= 65	3.9	3.3
Nausea, vomiting	< 65	7.8	5.7
	>= 65	4.1	3.7
Abdominal pain, distension, bloating, spasm, IBS	< 65	7.5	2.8
	>= 65	6.2	6

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, studyID=6002-US-005, 6002-0608, 6002-009, 6002-US-013. Grouped by USUBJID, AEDECOD, and TRPO1A. *Denominator: All IST <65 years: 346; All IST ≥ 65 Years: 388; Placebo <65 Years: 211; Placebo ≥ 65 Years: 215.

Table 49. Treatment-Emergent Adverse Events, Grouped Occurring by Age Group <75 versus ≥ 75 Years in Pool 8.

Treatment-emergent Adverse Events, grouped	Age Group (years)*	All IST %	Placebo %
Dyskinesia	< 75	16.7	7.5
	>= 75	8.6	7.3
Fall, dizziness, balance disorder	< 75	7.5	8.1
	>= 75	12.9	12.7
Dyspepsia, N, V, indigestion, epigastric pain,	< 75	7.3	4.6

Treatment-emergent Adverse Events, grouped	Age Group (years)*	All IST %	Placebo %
gastritis, duodenitis	>= 75	6.5	14.5
Insomnia, sleep disturbance, abnormal dreams	< 75	5.3	4.3
	>= 75	4.3	7.3
Nausea, vomiting	< 75	5.9	4.3
	>= 75	5.4	7.3
Abdominal pain, distension, bloating, spasm, IBS	< 75	7.2	3.5
	>= 75	4.3	10.9

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, studyID=6002-US-005, 6002-0608, 6002-009, 6002-US-013. Grouped by USUBJID, AEDECOD, and TRPO1A. *Denominator: All IST <75 years: 641; All IST ≥ 75 Years: 93; Placebo <75 Years: 371; Placebo ≥ 75 Years: 55.

The incidence of falls was 5.4% per istradefylline-treated subjects aged ≥75 years compared with 1.7% in subjects aged <65 years. The following table shows the TEAE of Fall by age group in Pool 8.

Table 50. Treatment-Emergent Adverse Event of Falls Occurring by Age Group in Pool 8.

Age Group (years)*	All IST %	Placebo %
< 65	1.7	4.7
>= 65	3.1	6
< 75	2	4.9
>= 75	5.4	9.1

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, studyID=6002-US-005, 6002-0608, 6002-009, 6002-US-013. Grouped by USUBJID, AEDECOD, and TRPO1A. *Denominator: All IST <65 years: 346; All IST ≥ 65 Years: 388; Placebo <65 Years: 211; Placebo ≥ 65 Years: 215, All IST <75 years: 641; All IST ≥ 75 Years: 93; Placebo <75 Years: 371; Placebo ≥ 75 Years: 55.

For race, Asian and White race made up the largest percentage of the population. The other populations had too few subjects to make a meaningful comparison. Dyskinesias occurred in a higher percentage of Whites compared to Asian (20.2% versus 11.7%, respectively). Fall/Dizziness/Balance Disorder occurred in a higher percentage of Whites compared to Asian (15.3% versus 3.1%, respectively). Dyspepsia/Nausea/Vomiting/Indigestion/Epigastric Pain/Gastritis/Duodenitis occurred in a higher percentage of Whites compared to Asian (10.9% versus 4.3%, respectively). Nausea/Vomiting occurred in a higher percentage of Whites

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compared to Asian (9.5% versus 2.7%, respectively). Insomnia, Sleep Disturbance, Abnormal Dreams occurred in a higher percentage of Whites compared to Asian (10.9% versus 2.3%, respectively).

Table 51. Incidence of Dyskinesia by Race in Pool 1.

Race	IST 10 mg %	IST 20 mg %	IST 40 mg %	IST 60 mg %	All IST %	Placebo %
Asian	50	11.1	11.6	33.3	11.7	4.5
White	21	18	21.1	24.6	20.2	11.3

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A. See Appendix Table 1 for denominators by race and dose.

Table 52. Incidence of Fall, Dizziness, Balance Disorder by Race in Pool 1.

Race	IST 10 mg %	IST 20 mg %	IST 40 mg %	IST 60 mg %	All IST %	Placebo %
Asian	25	3.2	2.4	33.3	3.1	3.4
White	12.6	14.8	15.4	19.7	15.3	12

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A. See Appendix Table 1 for denominators by race and dose.

Table 53. Incidence of Dyspepsia, Nausea, Vomiting, Indigestion, Epigastric Pain, Gastritis, Duodenitis by Race in Pool 1.

Race	IST 10 mg %	IST 20 mg %	IST 40 mg %	IST 60 mg %	All IST %	Placebo %
Asian	25	3.6	4.8	0	4.3	3.4
White	11.9	8.7	9.6	23.9	10.9	7.6

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A. See Appendix Table 1 for denominators by race and dose.

Table 54. Incidence of Insomnia, Sleep Disturbance, Abnormal Dreams by Race in Pool 1.

Race	IST 10 mg %	IST 20 mg %	IST 40 mg %	IST 60 mg %	All IST %	Placebo %
Asian	25	2.8	1.7	0	2.3	3.1
White	11.2	9.9	11.3	12.7	10.9	6.3

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A. See Appendix Table 1 for denominators by race and dose.

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Table 55. Incidence of Nausea and Vomiting by Race in Pool 1.

Race	IST 10 mg %	IST 20 mg %	IST 40 mg %	IST 60 mg %	All IST %	Placebo %
Asian	0	2.8	2.7	0	2.7	2.8
White	7.7	7.7	8.4	23.2	9.5	6

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A. See Appendix Table 1 for denominators by race and dose.

Table 56. Incidence of Abdominal Pain, Distension, Bloating, Spasm, Irritable Bowel Syndrome by Race in Pool 1.

Race	IST 10 mg %	IST 20 mg %	IST 40 mg %	IST 60 mg %	All IST %	Placebo %
Asian	0	5.9	6.8	0	6.3	5.5
White	9.1	7	7.9	6.3	7.5	5.1

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A. See Appendix Table 1 for denominators by race and dose.

In Pool 8, dyskinesias occurred at a higher frequency in Whites compared to Asians (27.5 versus 10.2%, respectively). Nausea/Vomiting occurred at a higher frequency in Whites compared to Asians (12.0 versus 2.8%, respectively). This may be due to differences in concomitant medication use as domperidone was used for nausea and vomiting in the Japanese population. Insomnia/Sleep disturbance/Abnormal dream occurred at a higher frequency in Whites compared to Asians (11.2 versus 2.0%, respectively). Overall, Fall/Dizziness/Balance Disorder occurred at a higher frequency in Whites compared to Asians in both istradefylline and placebo groups; however, Whites in the istradefylline-treated group had a higher rate of Fall/Dizziness/Balance Disorder compared to Asians (21.5% versus 2.0%, respectively).

Table 57. Treatment-Emergent Adverse Events, Grouped Occurring by Race in Pool 8.

Treatment-emergent Adverse Events, grouped.	Race*	All IST %	Placebo %
Dyskinesia	Asian	10.2	3.6
	White	27.5	13.2
Fall, dizziness, balance disorder	Asian	2	2.4
	White	21.5	18

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Treatment-emergent Adverse Events, grouped.	Race*	All IST %	Placebo %
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	Asian	4.1	3.2
	White	13.7	10.2
Insomnia, sleep disturbance, abnormal dreams	Asian	2	2
	White	11.2	7.8
Nausea, vomiting	Asian	2.8	2.8
	White	12	7.8
Abdominal pain, distension, bloating, spasm, IBS	Asian	6.3	4.8
	White	7.7	4.2

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, studyID=6002-US-005, 6002-0608, 6002-009, 6002-US-013. Grouped by USUBJID, AEDECOD, and TRPO1A. *Denominator: All IST Asian: 492; All IST White: 233; Placebo Asian: 251; Placebo White: 167.

For region, a higher incidence of Insomnia/Sleep Disturbance/Abnormal Dreams was seen in istradefylline-treated subjects in North America compared to outside of North America (11.2% versus 3.3%). A higher incidence of Abdominal Pain/Distention/Bloating/Spasm/IBS was seen in istradefylline-treated subjects in North America compared to outside of North America (7.7% versus 5.9% ,respectively). A higher incidence of Nausea/Vomiting was seen in istradefylline-treated subjects in North America compared to outside of North America (8.2% versus 3.2%, respectively).

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Table 59. Treatment-Emergent Adverse Events, Grouped Occurring in Pool 1 by Region.

Treatment-emergent Adverse Events, grouped	Istradefylline								Placebo	
	10 mg N=153 %	20 mg N=530 %	20 mg N=339 %	40 mg N=384 %	40 mg N=512 %	60 mg N=155 %	All N=1222 %	All N=851 %	N=513 %	N=497 %
Region	NA	NA	O	NA	O	NA	NA	O	NA	O
Dyskinesia	21.6	20.2	9.7	26	11.5	23.9	19.6	10.8	14.6	4.4
Fall, dizziness, balance disorder	14.4	16.4	2.9	19.8	3.9	20.6	15.1	3.5	15	3.8
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	11.8	10.2	2.9	10.9	6.1	23.2	9.3	4.8	8.6	3.8
Insomnia, sleep disturbance, abnormal dreams	11.8	11.9	1.8	14.6	4.3	11.6	11.2	3.3	8.2	2.8
Nausea, vomiting	7.2	9.1	2.4	10.7	3.7	22.6	8.2	3.2	6.8	2.8
Abdominal pain, distension, bloating, spasm, IBS	9.2	8.3	5	9.4	6.4	5.8	7.7	5.9	5.3	5.2

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, grouped on USUBJID and TRP01A. NA: North America, O: Outside North America.

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Sponsor's Analysis

The sponsor analyzed adverse events by gender, age group, race, and region and found differences in the incidence and severity of TEAEs reported.

For gender, a higher incidence of TEAEs leading to discontinuation in female subjects compared to male subjects for Pools 1, S1, and S2. The difference in incidence between istradefylline- and placebo-treated subjects was small (<5%). Male subjects had a higher incidence of serious TEAEs and severe TEAEs compared to female subjects in Pools 1, S1, and S2; however, the difference was small (< 5%). Female subjects had a higher incidence above placebo of dyskinesias as compared to male subjects in Pool 1 (12% versus 7%, respectively).

For age, serious TEAEs and severe TEAEs were more frequently reported in subjects ≥65 years and ≥75 years compared to subjects < 65 years and subjects < 75 years, respectively in Pools 1, S1, and S2. In Pools S1 and S2, older subjects had higher incidence of TEAEs leading to discontinuation compared to younger subjects. Subjects ≥75 years of age had a higher difference from placebo incidence of fall compared to subjects <65 years (3% versus 0%, respectively). Subjects ≥65 years of age had a higher incidence above placebo of dyskinesias compared to subjects <65 years of age (10% versus 7%, respectively).

For race, Whites had a higher incidence above placebo of experiencing any TEAE compared to Asians in Pool 1 (8% versus 4%, respectively). Asians had a higher incidence above placebo of experiencing a TEAE leading to discontinuation compared to Whites in Pools 1, S1, and S2. The overall difference in incidence of experiencing a TEAE leading to discontinuation from placebo between Asians and Whites was small (no higher than 3%). Asians had a higher incidence above placebo of experiencing an SAE or serious AE compared to Whites in Pools 1, S1, and S2 however the overall difference was small (<3%).

For region, the overall incidence of TEAEs reported in istradefylline-treated subjects was higher in North America compared to Pool S2 which occurred outside North America (81% versus 61%, respectively) however the difference from placebo was similar between the two groups. Pool S2 had a lower difference from placebo incidence of the TEAE of dizziness compared to North America (0% versus 2%, respectively).

In summary, female subjects had a higher incidence of dyskinesias compared to male subjects in Pool 1. Male subjects had a higher incidence of serious and severe TEAEs compared to female subjects. Older subjects had a higher incidence of serious and severe TEAEs compared to younger subjects. A higher incidence of falls was seen in subjects ≥75 years of age compared to subjects <65 years of age. Dyskinesias occurred at a higher frequency in subjects ≥65 years of age compared to subjects <65 years of age. Whites reported a higher incidence of TEAEs compared to Asians in Pool 1. Asians had a higher incidence above placebo of SAEs and serious AEs compared to Whites. Whites had a higher incidence of Dyskinesias, Fall/Dizziness/Balance Disorder, Dyspepsia/Nausea/Vomiting/Indigestion/Epigastric pain/Gastritis/Duodenitis,

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Nausea/Vomiting, and Insomnia/Sleep Disturbance/Abnormal Dream. The region of North America reported a higher incidence of dizziness compared to regions outside of North America. A higher incidence of Insomnia/Sleep Disturbance/Abnormal Dreams, Abdominal Pain/Distension/Bloating/Spasm/IBS, and Nausea/Vomiting were seen in the region of North America compared to outside of North America.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

I did not identify a safety signal for human carcinogenicity in a search of TEAEs belonging to the SOC Neoplasm.

In Pool 1, 16 istradefylline-treated subjects experienced at least one TEAE belonging to the SOC of Neoplasm. A total of 16 TEAEs belonging to the SOC of Neoplasm were reported in Pool 1 of which there were 11 unique preferred terms. The following preferred terms were reported: Adenocarcinoma; Basal Cell Carcinoma (n=5); Bile Duct Cancer; Bladder Neoplasm; Intraductal Papilloma Of Breast Neoplasm; Oral Neoplasm; Parathyroid Tumour Benign; Prostate Cancer (n=2); Rectal Cancer; Seborrhoeic Keratosis. The following table shows incidence of a subject experiencing at least one TEAE belonging to the SOC Neoplasm in Pool 1 by dose. The incidence of TEAEs related to neoplasm was similar between istradefylline- and placebo-treated subjects (0.8% versus 0.7%, respectively).

Table 58. Incidence of A Subject Experiencing at Least One TEAE Belonging to the SOC of Neoplasm by Dose in Pool 1.

IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	All IST N=2073 %	Placebo N=1010 %
0	0.6	0.9	1.9	0.8	0.7

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y, AESOC=neoplasm, grouped on USUBJID and TRP01A.

In Pool 2, 110 istradefylline-treated subjects reported at least on TEAE belonging to the SOC of Neoplasm (incidence of 5.8% (110/1893)). The following table shows incidence of TEAEs belonging to the SOC Neoplasm occurring in istradefylline-treated subjects by dose. Higher rates of TEAEs are seen compared to Pool 1 however this is likely in part due to the longer duration of the studies in Pool 2.

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Table 59. Incidence of A Subject Experiencing at Least One TEAE Belonging to the SOC Neoplasm by Dose in Pool 2.

IST 20 mg N=60 %	IST 40 mg N=1501 %	IST 60 mg N=332 %	All N=1893 %
0	5.4	8.7	5.8

Reviewer created table from the ISS ADAE dataset with ANL02FL=Y, SAFP02FL=Y, AESOC=Neoplasm, grouped on USUBJID, and TRP02A.

A total of 118 unique TEAEs (a subject was only counted once if the subject experienced the same preferred term more than once) were reported. The 118 unique TEAEs were comprised of 54 unique preferred terms. The following table shows incidence of subject reporting a unique TEAEs belonging to the SOC Neoplasm by Dose in Pool 2.

Table 60. TEAEs Belonging to the SOC Neoplasm by Dose in Pool 2.

MedDRA (Preferred term)	IST 20 mg N=60 %	IST 40 mg N=1501 %	IST 60 mg N=332 %	All N=1893 %
Basal Cell Carcinoma	0	1.1	2.4	1.3
Prostate Cancer*	0	0.4	1.4	0.4
Squamous Cell Carcinoma Of Skin	0	0.4	0	0.3
Seborrhoeic Keratosis	0	0.2	0.6	0.3
Malignant Melanoma	0	0.3	0.3	0.3
Squamous Cell Carcinoma	0	0.3	0.3	0.3
Lipoma	0	0.3	0	0.3
Haemangioma	0	0.2	0.3	0.2
Neoplasm Prostate*	0	0.2	0.5	0.2
Melanocytic Naevus	0	0.2	0	0.2
Neoplasm	0	0	0.6	0.1
Breast Cancer	0	0.1	0.3	0.1
Benign Breast Neoplasm	0	0.1	0	0.1
Benign Neoplasm Of Thyroid Gland	0	0.1	0	0.1
Skin Papilloma	0	0.1	0	0.1
Thyroid Adenoma	0	0.1	0	0.1
Benign Neoplasm Of Skin	0	0	0.3	0.1
Benign Ovarian Tumour*	0	0	0.9	0.1
Breast Cancer Male*	0	0	0.5	0.1
Colon Cancer	0	0	0.3	0.1

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MedDRA (Preferred term)	IST 20 mg N=60 %	IST 40 mg N=1501 %	IST 60 mg N=332 %	All N=1893 %
Essential Thrombocythaemia	0	0	0.3	0.1
Keratoacanthoma	0	0	0.3	0.1
Neoplasm Malignant	0	0	0.3	0.1
Neuroma	0	0	0.3	0.1
Oesophageal Carcinoma	0	0	0.3	0.1
Prostate Cancer Metastatic*	0	0	0.5	0.1
Thyroid Cancer	0	0	0.3	0.1
Acrochordon	0	0.1	0	0.1
Acute Myeloid Leukaemia	0	0.1	0	0.1
Bladder Cancer	0	0.1	0	0.1
Bladder Neoplasm	0	0.1	0	0.1
Bladder Transitional Cell Carcinoma	0	0.1	0	0.1
Colon Adenoma	0	0.1	0	0.1
Fibrous Histiocytoma	0	0.1	0	0.1
Gastric Cancer	0	0.1	0	0.1
Gastrointestinal Stromal Tumour	0	0.1	0	0.1
Haemangioma Of Liver	0	0.1	0	0.1
Hypopharyngeal Neoplasm	0	0.1	0	0.1
Intracranial Tumour Haemorrhage	0	0.1	0	0.1
Intraductal Papilloma Of Breast	0	0.1	0	0.1
Large Intestine Benign Neoplasm	0	0.1	0	0.1
Meningioma	0	0.1	0	0.1
Metastases To Central Nervous System	0	0.1	0	0.1
Monoclonal Gammopathy	0	0.1	0	0.1
Nasal Cavity Cancer	0	0.1	0	0.1
Non-Hodgkin's Lymphoma	0	0.1	0	0.1
Oesophageal Adenocarcinoma	0	0.1	0	0.1
Oral Neoplasm	0	0.1	0	0.1
Pancreatic Carcinoma	0	0.1	0	0.1
Rectal Adenoma	0	0.1	0	0.1
Renal Cancer	0	0.1	0	0.1
Skin Cancer	0	0.1	0	0.1
Small Cell Lung Cancer	0	0.1	0	0.1
Waldenstrom's Macroglobulinaemia	0	0.1	0	0.1

Reviewer created table from the ISS ADAE dataset with ANL02FL=Y, SAFP02FL=Y, AESOC=Neoplasm, grouped on USUBJID, AEDECOD and TRP02A. If a subject experienced the same preferred term more than once, the subject was only counted once for that preferred term. *Rates adjusted for female and male populations.

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Reviewer comment: No neoplasm had incidence > 1% except for basal cell cancer. In a retrospective cohort study among non-Parkinson's disease patients in the United States, Goldenberg et al. calculated the incidence of basal cell carcinoma to be 31.4% among patients age 55 to 64 years.[3] Patients with Parkinson's disease are recognized to be at higher risk for developing basal cell carcinoma compared to the average population. In a retrospective cohort study by Lerman, S. et al., patients with Parkinson's disease were observed to have an increased odds ratio of developing basal cell carcinoma of 1.5 to 2.1.[4] Overall, these findings do not support a safety signal of basal cell cancer with istradefylline use.

In Pool 3, there was one TEAE related to neoplasm occurring in an istradefylline-treated subject (Basal Cell Neoplasm) compared to one TEAE in a placebo-treated subject (incidence of 0.7% versus 1.5%, respectively).

No TEAEs related to neoplasm were reported in Pool 4.

In Study 6002-018, there was one TEAE of breast cancer (incidence of 0.4%).

The sponsor notes that in the postmarketing setting, 12 adverse events belonging to the SOC Neoplasm were reported leading to an event rate of 0%.

Overall, no safety signal was identified for human carcinogenicity with istradefylline.

8.8.2. Human Reproduction and Pregnancy

There are limited safety data on the use of istradefylline in pregnant women or in women exposed via a male partner treated with istradefylline.

The sponsor notes that one pregnancy was reported among participants in clinical studies that was previously summarized in Dr. Podskalny's review of the original submission. No complications were reported with this case. No cases of pregnancy were reported in the sponsor's postmarketing safety review.

Reviewer comment: There is limited information on the effects of istradefylline during pregnancy.

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[3] Goldenberg G, Karagiannis T, Palmer J, et. al. Incidence and prevalence of basal cell carcinoma (BCC) and locally advanced BCC (LABCC) in a large commercially insured population in the United States: A retrospective cohort study. *J Am Acad Dermatol*. 2016 Nov;75(5):957-966.e2. doi: 10.1016/j.jaad.2016.06.020. Epub 2016 Jul 26.
[4] Lerman S, Amichai B, Weinstein G, et al. Parkinson's Disease, Melanoma, and Keratinocyte Carcinoma: A Population-Based Study. Neuroepidemiology. 2018;50(3-4):168-173. doi: 10.1159/000487855. Epub 2018 Mar 22.

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8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The sponsor performed a review for cases of overdose, drug abuse potential, withdrawal and rebound and did not find a safety signal.

Overdose

The sponsor reported two TEAEs of overdose that occurred with two subjects enrolled in the clinical trials. Both cases involved accidental overdoses. One case (6002-US-(b) (6), formerly (b) (6), Case Mfr. Report #KW-6002-(b) (6)) was summarized in the review by Dr. Podskalny at the time of the original submission and involved an accidental overdose of six tablets of istradefylline along with alcohol. The patient experienced hallucinations, agitation, and dyskinesia. The second case (6002-US-(b) (6)/formerly (b) (6)) involved a 72-year-old male subject who reported an accidental overdose on Study Day 206 without any associated TEAEs. The subject continued on in the study and no further details were given regarding the case.

There was one additional case that was summarized in Dr. Podskalny's review of the original submission. The case was related to accidental ingestion of a single 40 mg tablet with istradefylline by a 3-year-old son of a subject (Subject ID (b) (6)) without reported adverse effects.

Abuse Potential

Please refer to the Controlled Substances Staff review of the sponsor's human abuse potential study.

I searched Pool 1 for TEAEs related to abuse potential (with preferred terms as noted in the Guidance for the Assessment of Abuse Potential of Drugs) and found two terms to have an incidence of 2% greater than placebo: Hallucinations and Confusional State. The following table shows incidence by dose for Hallucinations and Confusional State in Pool 2. The difference from placebo was no higher than 4% for either term.

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Table 61. TEAEs Related to Abuse Potential with Incidence of at Least 2% Greater than Placebo in Pool 1.

MedDRA (preferred term)	IST 10 mg N=153 %	IST 20 mg N=869 %	IST 40 mg N=896 %	IST 60 mg N=155 %	Placebo N=1010 %
Hallucination	1.3	2.1	2.9	5.8	1.8
Confusional State	3.3	0.7	0.6	1.3	0.2

Reviewer created table using the MAED tool and the ISS ADAE dataset with TRTEMFL=Y, ANL01FL=Y, SAFP01FL=Y.

Withdrawal and Rebound

The sponsor did not find evidence that istradefylline is associated with withdrawal or rebound symptoms.

No clinical studies have been conducted to evaluate the withdrawal or rebound effect of istradefylline.

Of note, subjects were not tapered off of study drug. With regards to withdrawal symptoms, protocols in Pool 1 studies did not require post-study safety observation of all subjects. In Pool 2, SAEs were required to be reported in most studies for up to 30 days after the last dose of study drug. I reviewed adverse events for Pools 1 and 2 and did not find any TEAEs of withdrawal syndrome. The sponsor concluded that a low likelihood for developing withdrawal symptoms exists given the relatively long elimination half-life of istradefylline (82.7 to 148.3 hours).

With regards to rebound symptoms, the sponsor searched Pool 1 for adverse events with rebound potential occurring within 40 days of discontinuation with istradefylline. AEs of rebound potential included AEs related to constipation, nausea, falls, fractures, contusions, joint/muscle/musculoskeletal stiffness, movement disorder-related events, hallucinations, insomnia, and sleep disorder.

The results of the sponsor's search showed no imbalance in the incidence of AEs of withdrawal potential between istradefylline- and placebo-treated subjects. Potential underreporting of events may have occurred as non-serious AEs occurring after the last dose of istradefylline were not required to be reported.

Overall, a safety signal for AEs related to withdrawal and rebound was not found. Limitations to the analysis for a safety signal include absence of a post-study safety observation period for most subjects in Pool 1.

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8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

As of October 31, 2018, the cumulative postmarketing exposure estimate based on Japanese sales data is 56,000 patients. The sponsor notes that review of postmarketing cases did not identify any new safety signals for istradefylline.

Event frequency of adverse events and adverse events by SOC was less than 1%.

8.9.2. Expectations on Safety in the Postmarket Setting

PMRs to study the effects of istradefylline during pregnancy and on pregnancy outcomes will help to address the lack of adequate information on the safety of istradefylline in pregnancy.

8.9.3. Additional Safety Issues From Other Disciplines

Please see other disciplines' review.

8.10. Integrated Assessment of Safety

Safety findings from NDA 022075 are summarized below.

Deaths. There were 39 deaths occurring in subjects who received istradefylline in the current submission combined with the original submission. There was not an excess of deaths in istradefylline-treated groups compared to placebo-treated groups. The causes of death were consistent with expected causes of death for the age group and disability caused by PD.
SAE. The evaluation of SAEs did not identify any significant safety issued with istradefylline. Infections and fracture occurred slightly more frequently in subjects who received istradefylline compared to subjects who received placebo, all less than 1%.
AE leading to drug or study discontinuations. The rates for discontinuations due to adverse events were greater for subjects who received istradefylline than for subjects who received placebo with evidence of a dose response in Pools 1 and 8. The most frequent AEs causing discontinuation belonged to the groupings Nausea/Vomiting and Psychosis/Delusions/Hallucinations. The most frequent AEs causing discontinuation in Pool 8 was similar to Pool 1 and were Psychosis/Delusions/Hallucinations.
Significant AEs. Evaluation of severe AEs did not identify a new safety signal.
Most common AE. The most common AE for the 20 mg and 40 mg dose of istradefylline in Pool 1 belonged to the groupings Dyskinesias, Dyspepsia/Nausea/Vomiting/Indigestion/Epigastric Pain/Gastritis/Duodenitis, and Insomnia/Sleep Disturbance/Abnormal Dreams and occurred in up to 17.7%, 8.1%, and 8.7%, respectively, of subjects given istradefylline. A dose response was not seen. Pool 8 had similar findings. The most common AE in istradefylline-treated subjects in Pool 8 belonged to the Dyskinesia, Infection, Fall/Dizziness/Balance disorder and occurred in

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16%, 14%, and 8%, respectively, of istradefylline-treated subjects.
Vital sign, laboratory and ECG evaluations showed small mean increases in systolic blood pressure 0.3 mmHg in Pool 8) in subjects who received istradefylline. In Pools S1 and S2, more subjects who received istradefylline had decreases in body weight compared to subjects who received placebo. Laboratory and ECG evaluations did not identify a signal.
Pre-specified AE of interest

- Impulse control Disorder – Istradefylline-treated subjects had similar incidence of TEAEs related to impulse control disorder compared to placebo-controlled subjects in Pool 1 (difference <1%); however, all cases of impulse control disorder (13 cases) occurred in istradefylline-treated subjects compared to no cases in placebo. QUIP-RS scores were not higher at 12-weeks compared to baseline scores. There were two postmarketing reports of impulse control disorder that occurred within 10 days of initiation with istradefylline, with one case having resolution of symptoms with cessation of istradefylline.
- Dizziness- Istradefylline-treated subjects had a higher incidence of TEAEs related to dizziness compared to placebo-controlled subjects in Pool 1 (incidence 5.7% all doses combined versus 4.2%, respectively). Similar findings were observed in Pool 8
- Falls – Subjects who received istradefylline had similar incidence of falls as compared to subjects who received placebo (8.0% versus 7.6%, respectively).
- Effects on Ability to Drive – Istradefylline-treated subjects reported a similar incidence of Road Traffic Accidents as placebo-treated subjects.
- Cardiac Safety - No cardiac safety signal was identified. Istradefylline-treated subjects had a similar incidence of TEAEs related to the Cardiology SOC and TEAEs of potential ischemic etiology as compared to placebo-treated subjects (3.0% versus 3.5% and 4% versus 5.3%, respectively).
- Suicidal Behavior - There was no evidence of an increased risk of suicidality with istradefylline.
- Neutropenia and Neutropenic Sepsis - No signal for neutropenia or neutropenic sepsis was identified.

9. Advisory Committee Meeting and Other External Consultations

There was no FDA AC meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

I recommend that Dyskinesias, Psychosis/Delusions/Hallucinations, and Impulse Control Disorder be added as a Warnings and Precautions statement to the label.

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10.2. Nonprescription Drug Labeling

Not Applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Not Applicable.

12. Postmarketing Requirements and Commitments

None.

13. Appendices

13.1. References

13.2. Denominator by Dose and Race in Pool 1 for Safety Analysis by Demographic Subgroup.

Table 62. Denominator by Dose and Race in Pool 1 for Safety Analysis by Demographic Subgroup.

Race	IST 10 mg	IST 20 mg	IST 40 mg	IST 60 mg	All IST	Placebo
Asian	4	253	294	3	554	290
White	143	596	573	142	1454	681

Reviewer created table from the ISS ADAE dataset with ANL01FL=Y, SAFP01FL=Y.

13.3. Financial Disclosure

The reader is referred to the review of clinical efficacy by Dr. Leonard Kapcala for financial

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disclosures.

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/s/

NATALIE M BRANAGAN
08/27/2019 09:13:53 AM

SALLY U YASUDA
08/27/2019 09:15:21 AM

CLINICAL REVIEW OF EFFICACY

Application Type	Re-Submission of NDA (Response to Non-Approvable Letter)
Application Number(s)	22075
Priority or Standard	Standard
Submit Date(s)	2/27/19
Received Date(s)	2/27/19
PDUFA Goal Date	8/27/19
Division/Office	DNP/ODE 1
Reviewer Name(s)	Leonard P. Kapcala, M.D.
Review Completion Date	7/26/19
Established/Proper Name	ISTRADEFYLLINE
(Proposed) Trade Name	NOURIANZ
Applicant	KYOWA KIRIN INC
Dosage Form(s)	Tablets 20 mg, 40 mg
Applicant Proposed Dosing Regimen(s)	Administer 20 mg orally once daily. The dose may be increased to 40 mg once daily based on (b) (4)
Applicant Proposed Indication(s)/Population(s)	Adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "OFF" episodes
Recommendation on Regulatory Action	I recommend against approval and for issuing a Complete Response letter
Recommended Indication(s)/Population(s) (if applicable)	Not applicable because I am not recommending approval

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Glossary

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AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics

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PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

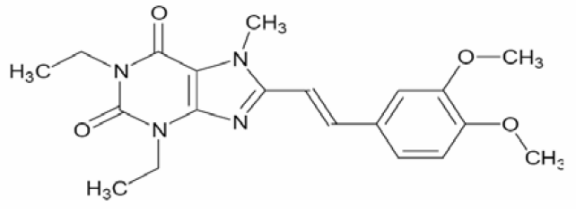
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1. Executive Summary

1.1. Product Introduction

The established name for the product of Kyowa's NDA application is Istradefylline the sponsor has not proposed a trade name at the time of this review. The drug substance appears as light yellow-green, needle-shaped crystals.

Figure 1 Chemical Structure of Istradefylline



Chemical Name (IUPAC)
(E)-8-(3,4-Dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione

Molecular Formula: $C_{20}H_{24}N_4O_4$

Molecular Weight: 384.43

The investigational drug product consists of 20 mg and 40 mg tablets of Istradefylline Lactose, (b) (4) crospovidone, polyvinyl alcohol and (b) (4). They are biconvex shaped, peach colored, film coated tablets.

Storage at 20°C to 25°C (68°F-77°F) is recommend; excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].

Chemical Class
Istradefylline is a New Molecular Entity (NME) an Adenosine A2A receptor antagonist.

Pharmaceutical Class
A2A receptors are expressed mainly on the axon terminals of medium spiny neurons (MSNs) in the striatum and the globus palidus externa (GPe). Their function in modulating the activity in the indirect pathway is discussed in detail in section 5. The net effect of Adenosine A2A receptor activation results in GABAergic input to the globus pallidus interna (GPi) and eventually to the thalamus and areas motor cortex. Antagonism of Adenosine A2A receptors is expected to reduce the inhibitory out from the GPi to the thalamus and eventually to areas of cortex reducing the hypokinetic motor symptoms of PD.

1.2. Conclusions on the Substantial Evidence of Effectiveness

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Given all my concerns which I have summarized in my Benefit-Risk Integrated Assessment and Benefit section of the Benefit-Risk table and have also outlined in more detail in other sections of my review, I am unable to conclude there is substantial evidence for the effectiveness of istradefylline and am not confident that istradefylline will have the effect purported to have in the label for patients in the U.S. in accordance with 21CFR 314.125.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Given all my concerns which I have summarized in the table below regarding benefit and discussed in more detail in other sections of my review, I am unable to conclude there is substantial evidence for the effectiveness of istradefylline and am not confident that istradefylline will have the effect purported to have in the label for patients in the U.S. in accordance with 21CFR 314.125.

Furthermore, it is not possible to exclude the possibility that Japanese patients exhibit an increased sensitivity/responsiveness to istradefylline.

My main reasons for not being able to conclude that there is substantial evidence for effectiveness of istradefylline are:

- Most results for efficacy for many endpoints from 8 pivotal trials do not support the efficacy of istradefylline.

- The new supporting data for istradefylline efficacy comes solely from two Japanese trials. The results of these trials were known in 2012 when the Agency met with the sponsor and recommended conducting a new trial by attempting to treat patients who had been "optimally" treated for Parkinson's disease. The Agency had recommended this new trial (which the sponsor did conduct as Study 014) because it did not consider the results of the two Japanese trials to be adequate to support a re-submission of the NDA.

- Significant majorities (57 % - 40 mg; 72 % - 20 mg) of all patients treated with 20 mg and 40 mg istradefylline were studied in 5 pivotal trials which failed to demonstrate efficacy of istradefylline. When consideration was given to all patients outside of Japan who were enrolled in the 5 failing trials, the percentages (80 % - 40 mg; 100 % - 20 mg) were considerably higher indicating that there is relatively little evidence outside of Japan for supporting efficacy of istradefylline. It is also noteworthy that the only data outside of Japan supporting istradefylline comes from Study 005 which had been reviewed in the original NDA submission and which was not considered sufficient to support the efficacy of istradefylline.

- Overall, the best efficacy for istradefylline was observed in the Japanese pivotal trials. Efficacy in pools of all pivotal trials outside of Japan is much lower (~ 60-70 %) for important efficacy endpoints compared to results in a pool of the Japanese trials. Of potentially great significance to me also is the fact that it is not possible to exclude the possibility that Japanese patients exhibit an increased sensitivity/responsiveness to istradefylline compared to patients outside of Japan because of genetic/racial factors in the Japanese patients.

- Results of 3 large pivotal trials (007, 014, 018) studying a range of doses (10 mg, 20 mg, 40 mg) are particularly troubling because their efficacy results were completely negative for important efficacy endpoints. In Study 018, the mean treatment difference for ON time

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without troublesome dyskinesia (i.e., the most important efficacy endpoint indicating a direct therapeutic benefit to a patient) and for OFF time frequently suggested a worsening effect on these endpoints. All 3 trials also showed essentially a 0 effect on ON time without troublesome dyskinesia for the 40 mg dose (the highest dose the sponsor proposes for marketing). This is an observation I cannot recall ever seeing during my review of drugs for Parkinson's disease for more than 20 years. Of note, Study 014 had been conducted after close collaborative planning with the Agency to attempt to enroll "optimally" treated Parkinson's disease patients and show an additional therapeutic benefit from istradefylline treatment. Although Study 014 was the largest pivotal trial relative to size of each treatment group (nearly 200 patients per arm), this trial failed to show any evidence of efficacy for istradefylline.

- Subgroup/subpopulation analyses suggest that there is a progressive decrease of efficacy as weight increases and that efficacy can be completely lost for patients at or above 85 kg (187 lbs). This effect is most clearly associated with patients outside of Japan. The effect of weight was not clear for Japanese patients because those patients were not well distributed throughout the 4 weight subgroup categories. The effect of weight is not related to a decrease in istradefylline exposure as weight increases.

- I also share the concerns which had been outlined previously by the FDA during the original NDA review and issuance of the Non-Approvable letter regarding the potential for no benefit or a weak effect of istradefylline. If patients used istradefylline and experienced no benefit or weak effects instead of another clearly effective adjunctive treatment, they could expose themselves to a serious risk such as a fall resulting in a hip fracture with potentially associated serious consequences on morbidity and even mortality.

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Benefit-Risk Dimensions Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The condition treated was advanced Parkinson's disease which is operationally defined as patients taking levodopa and experiencing OFF episodes. Istradefylline was given to these patients as adjunctive treatment.	The pivotal trials were adequate for investigating effects on istradefylline on adult patients with advanced Parkinson's disease.
Current Treatment Options	• There are many approved treatments as adjunctive therapy for patients with advanced Parkinson's disease. These treatments, which have **symptomatic** benefits, consist of dopaminergic agonists, inhibitors of monoamine oxidase B (MAO-B, inhibitors of catechol-O-methyltransferase (COMT), and amantadine. Overall, the benefit (relative to placebo in pivotal trials) of these approved products for decreasing total OFF time ranges from approximately 0.5 hours to 2 hours. • As the disease progresses, patients on levodopa often add one of these classes of drug. Over time as the disease continues to progress, patients frequently add a drug from another class such that many patients eventually are taking drugs from 2 or 3 of these classes in addition to levodopa. Some of the most severe patients may eventually take their levodopa as intestinal infusion over the day in addition to these other classes of drugs. • None of these drugs have been shown to be superior to another drug for treating OFF time, nor to provide additional benefit in patients who have been documented to have been optimally treated. Neither have any of these been shown to slow disease progression. • The goal of Study 014 was to demonstrate efficacy of istradefylline in a population of patients who supposedly had been “optimally” treated	Study 014 was not successful for demonstrating that istradefylline could provide an additional therapeutic benefit to patients with advanced Parkinson's disease who were taking levodopa and potentially various combinations of other approved drugs for treating OFF time. Istradefylline does not provide any additional benefit over that of other drugs approved for symptomatic treatment of advanced Parkinson's disease. Considering across study comparisons, the magnitude of the benefit of istradefylline for treating OFF time in the few positive studies suggests that its seeming benefit would be at the lower end (e.g. treatment difference of 0.7 - 1.0 hrs OFF decrease) of the magnitude of benefit of these other approved adjunctive medications.

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Benefit-Risk Dimensions Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with a host of these approved medications. However, this study failed to demonstrate efficacy in this population.	
Benefit	• Istradefylline produced statistically significant (< 0.05) effects on the primary efficacy endpoint (percentage of daily awake OFF or total OFF) such as decreasing OFF time in 4 pivotal trials (005, 013, 0608, 009) according to the pre-specified statistical analysis. However, because a decrease in OFF could also be due to undesired effects on increasing troublesome dyskinesia or sleep time, I consider that the most important outcome to assess (in the context of a decrease in OFF) is an increase in ON time without troublesome dyskinesia which is a direct and true benefit for any patient. When this important outcome which corresponded to the primary efficacy endpoint (percentage change or total change) was assessed for statistical significance, I considered only 3 pivotal trials (005, 0608, 009) as "positive" for showing efficacy of 40 mg istradefylline. Although Study 009 was "positive" for showing efficacy of 20 mg istradefylline, Study 0608 was not "positive" for the 20 mg dose because there was not a statistically significant effect on increasing ON time without troublesome dyskinesia. • When the DNP met with the sponsor in 2012 to discuss a path forward for the sponsor with istradefylline (following the Non-Approvable letter), the Agency recommended that the sponsor attempt to show an additional benefit of istradefylline in "optimally" treated patients. Alternatively, the Agency noted that the sponsor could submit other data from patients who were not considered "optimally" treated but	Given all my concerns which I have summarized here and outlined in more detail in other sections of my review, I am unable to conclude there is substantial evidence for the effectiveness of istradefylline and am not confident that istradefylline will have the effect purported to have in the label for patients in the U.S. in accordance with 21CFR 314.125. I also share the concerns which had been outlined previously by the Agency regarding the potential for no benefit or a weak effect of istradefylline. If patients used istradefylline and experienced no benefit or weak effects instead of using another clearly effective adjunctive treatment, they could expose themselves to a serious risk such as a fall resulting in a hip fracture with potentially associated serious consequences on morbidity and even mortality.

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Benefit-Risk Dimensions Dimension	Evidence and Uncertainties	Conclusions and Reasons
	that these results should be "robust" not only for the primary efficacy endpoint but also for many secondary efficacy endpoints. The Agency was aware of the results of the 2 Japanese trials (0608, 009) at the time of the meeting and did not think that results of these trials were adequate for addressing Agency concerns about efficacy of istradefylline. As outlined in my review, all the new supporting data for efficacy are derived from these two Japanese trials. The efficacy in the pool of 6 pivotal trials conducted outside of Japan is approximately 60 -70 % lower than the efficacy for ON time without troublesome dyskinesia and for OFF time in the pool of the two Japanese trials. Furthermore, it is not possible to exclude the possibility that Japanese patients exhibit an increased sensitivity/responsiveness to istradefylline compared to patients outside of Japan because of genetic/racial factors. My concerns about the Japanese data serving as the main support for istradefylline efficacy, which was clearly lacking in the original NDA submission, are that the effects observed in Japan may not be applicable to patients outside of Japan and particularly to patients in the U.S. • I considered 5 pivotal trials (006, 007, 013, 014, 018) as failing to demonstrate efficacy of istradefylline for various doses (10 mg, 20 mg, 40 mg, 60 mg). These "failed" trials consisted of very large percentages of all patients studied in the 8 pivotal trials. Whereas a total of 879 patients had been treated with 40 mg istradefylline in all 8 pivotal trials, 57 % of that total were in these 5 "failed" trials. Considering that a total of 848 patients had been treated with 20 mg in all 8 pivotal trials, 72 % of this total were in these 5 "failed" trials. When these percentages are calculated relative to patients treated outside of Japan (because of my outlined concerns for the Japanese	

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Benefit-Risk Dimensions Dimension	Evidence and Uncertainties	Conclusions and Reasons
	data), 100 % (613/613) of the patients treated with 20 mg were in these 5 "failed" trials and 80 % (503/632) treated with 40 mg were in these 5 "failed" trials. Thus, a significant majority of patients in all pivotal trials (and greater majorities were applicable for trials outside of Japan) did not experience a therapeutic benefit from istradefylline for the 20 mg and 40 mg doses. In addition, Table 54 and Table 55 show that most of the efficacy for many Parkinson's disease endpoints are not statistically significant for the most of the results for all 8 pivotal trials. • In consideration of the failure of the 5 pivotal trials to support istradefylline efficacy, I am particularly troubled by the fact that 3 large trials (018, 007, 014) showed NO efficacy (i.e., essentially 0 treatment difference) for the most important efficacy endpoint, ON time without troublesome dyskinesia for the 40 mg dose. Furthermore, results in Study 018 which included 3 doses (10 mg, 20 mg, 40 mg) frequently showed numerical treatment difference results which suggested worsening of ON time without troublesome dyskinesia and of OFF time. I also consider the fact that Study 014 was completely negative for showing efficacy to be most concerning about istradefylline efficacy. Study 014 was the trial in which the sponsor followed the DNP recommendation and attempted to investigate istradefylline in an "optimally" treated Parkinson's disease population as a result of the 2012 meeting with the Agency. • As a result of subgroup/subpopulation analyses based upon 4 mutually exclusive weight categories, there appears to be a progressive decrease of efficacy for ON time without troublesome dyskinesia	

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Benefit-Risk Dimensions Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and for OFF time as weight categories increase. In many instances, efficacy based upon these endpoints is completely lost for the weight category (≥ 85 kg/187 lbs) and the mean treatment difference sometimes even shows a numerical worsening effect on these important efficacy endpoints. These effects were most clearly observed in patients outside of Japan. A weight effect was not clearly observed in the Japanese trials but most of the patients in these trials were in the 2 lowest weight categories. These results raise the question whether patients outside of Japan experience decreasing istradefylline efficacy as weight increases and that some "heavier" patients might not experience any efficacy from istradefylline. The explanation seems like it must be on pharmacodynamic basis because istradefylline exposure does not decrease as weight increases.	
Risk and Risk Management	Based upon the safety review of Dr. Natalie Branagan (refer to her review for details), there does not appear to be serious concerns about the safety of istradefylline.	There do not appear to be safety concerns for istradefylline which would preclude its approval.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	X Patient reported outcome (PRO)	1.4
	□ Observer reported outcome (ObsRO)	
	X Clinician reported outcome (ClinRO)	1.4
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

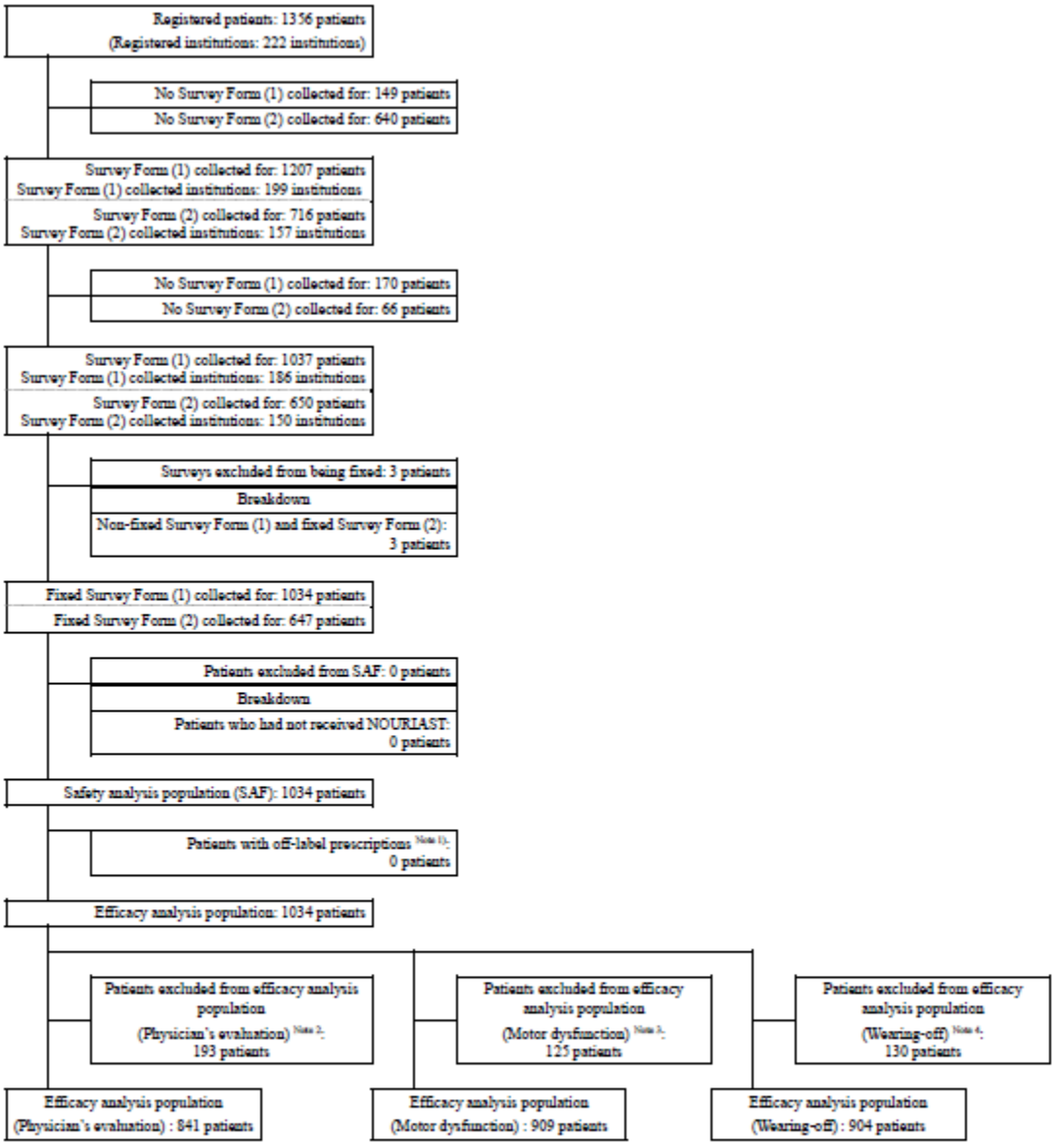
The sponsor submitted a Periodic Safety Report in which it noted that it was conducting a specified drug use-results survey (survey on long-term use) by the central registration method to collect 1,000 evaluable cases during the 6-year period from May 30, 2013 to May 31, 2019. The observation period for each patient is 1 year (or until the time of completion or discontinuation of treatment with NOURIAST if completed or discontinued within a year-long period).

The following information abstracted from this report present some noteworthy experience with istradefylline in Japan.

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The disposition of surveyed patients is shown in

Figure 2 Disposition of Survey Patients



Note 1) Except for patients with the indication of "improvement of the wearing-off phenomenon in Parkinson's disease patients treated with a levodopa-containing preparation"

Note 2) "Unassessable" for the efficacy of NOURIAST based on the physician's evaluation

Note 3) "Unassessable" for the assessment of motor dysfunction

Note 4) "Unassessable" for the assessment of the wearing-off phenomenon

The sponsor concluded a contract with 277 institutions (departments) by the end date (March 24, 2018) of the survey unit period. A total of 1,356 patients have been registered at 222 of the 277

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institutions (departments). Survey Forms (1) and Survey Forms (2) have been collected from 1034 patients and 647 patients, respectively. Because no patient was excluded from the safety or efficacy analysis, all 1034 patients with the locked Survey form (1) were included in the safety and efficacy analysis populations.

The following tables describe information obtained from the survey including dosing information, disposition of discontinued patients and perceptions of efficacy.

Table 1 Summary Statistics for Daily Dose and Duration of Treatment

Average daily dose Summary statistics (unit: mg) N=1029*	Mean	22.61
	Standard deviation	5.801
	Median	20.00
	Minimum – Maximum	15.7 – 40.0
Duration of treatment Summary statistics (unit: days) N=1034	Mean	264.8
	Standard deviation	129.52
	Median	364.0
	Minimum – Maximum	1 – 806

*: A patient (five patients) whose total daily dose was unknown is excluded from the tabulation.

Table 2 Nouriast (Istradefylline) Doses at 6 Months and 1 Year

	Timepoint	
	6 months	1 year
	N	N
20 mg	665	451
40 mg	139	129
Others	0	0

Table 3 Disposition of Discontinued Patients (A single patient may be counted in more than 1 category

	N
Discontinued patients	294
Adverse event	120
Death	11
General progression of the underlying disease (excluding rapid progression/aggravation)	27
Transfer to another hospital (excluding transient transfer)	53
Others	94

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Table 4 Efficacy of Nouriast (Istradefylline) Based upon the Phyisician's Evaluation

Efficacy based on the physician's evaluation	End of observation period
	Number of patients n (%)
Total	1034
Effective	643 (62.19)
Not-effective	198 (19.15)
Unassessable	193

Table 5 Efficacy Evaluation (Motor Dysfunction)

Efficacy evaluation (motor dysfunction)	Number of patients n (%)
Significantly improved	13 (1.26)
Improved	481 (46.52)
Unchanged	382 (36.94)
Worsened	33 (3.19)
Unassessable	125

Table 6 Efficacy Evaluation (Wearing OFF Phenomenon)

Efficacy evaluation (wearing-off phenomenon)	Number of patients n (%)
Significantly improved	15 (1.45)
Improved	451 (43.62)
Unchanged	427 (41.30)
Worsened	11 (1.06)
Unassessable	130

Table 7 Efficacy Evaluation (Wearing OFF Phenomenon, OFF Phase)

Efficacy evaluation (wearing-off phenomenon_OFF phase)	Number of patients n (%)
Decreased	358 (34.62)
Unchanged	493 (47.68)
Increased	11 (1.06)
Unassessable	172

Reviewer Comment(s)

- Considering that these assessments about "efficacy" are not blinded but apparently open-label assessments, they cannot truly reflect efficacy. Nevertheless, I will provide a few comments on these reported assessments,

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- I note that it is interesting that the physician's overall assessment of open-label "effectiveness" is considerably higher for "effective" rating than the other efficacy assessments of improved/significantly improved or decreased OFF.

- In these assessments, less than 50 % of patients are considered improved/significantly improved and only about one third of patient are assessed as having less OFF time. I do not conclude that these assessments lessen my concerns about relatively weak efficacy from istradefylline treatment.

- It is also noteworthy that considerable percentages of patients are considered unassessable.

Safety information was also assessed. However, I will not comment on this because my review focuses on efficacy.

2. Therapeutic Context

Analysis of Condition

Patients with advanced Parkinson's disease were included in the population studied for this NDA. Typically, many patients after 5 years of diagnosis and particularly after years of medical treatment are frequently considered at the stage of "advanced" Parkinson's disease. Advanced Parkinson's disease is often operationally defined as patients taking levodopa (usually with a dopa decarboxylase inhibitor) and are experiencing motor fluctuations such as "OFF" time. Protocols for studies in advanced Parkinson's disease typically require (in the inclusion criterion) a minimum amount of "OFF" time such as 2 or 3 hours daily based upon a minimum daily requirement or a minimum average daily requirement. Despite the fact that only 2-3 hours is required, most trials of advanced patient usually include patients with an average of 5-6 OFF hours daily. When patients with OFF episodes take another medication in addition to levodopa, the other treatment is considered adjunctive to levodopa. Istradefylline would clearly be considered an adjunctive treatment for Parkinson's disease.

Medical treatment of Parkinson's disease focuses on primarily medications which enhance dopaminergic tone so that these medications can help treat motor function which can be sensitive to dopaminergic drugs.

The pivotal trials in this NDA clearly studied patients with advanced Parkinson's disease.

2.1. Analysis of Current Treatment Options

Although the product is the first in a new proposed class (adenosine A2A receptor antagonist) of medications there are many marketed products sharing the same indication as the one sought by the sponsor for istradefylline. The medications listed below are marketed products with

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demonstrated efficacy indicated for the symptomatic treatment of PD. Table 8 shows the available drug options in the U.S. for treatment of advanced Parkinson's disease. Deep brain stimulation (DBS) is also an option for treating patients with advanced Parkinson's disease.

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Table 8 Medications Marketed in The U.S. for Adjunctive Treatment of Parkinson's Disease

Medication Class	Generic Name	Trade/Proprietary Name
Dopamine Replacement	Carbidopa/Levodopa CD/LD	Sinemet, Sinemet CR, Rytary
	Carbidopa/Levodopa CD/LD Gel (intestinal infusion)	Duopa
Dopamine Agonists	Bromocriptine (ergot)	Parlodel
	Pramipexole (non-ergot)	Mirapex
	Ropinirole (non-ergot)	Requip
	Apomorphine (non-ergot) injection	Apokyn
	Rotigotine (non-ergot) transdermal	Neupro
	Pramipexole Extended-Release (non-ergot)	Mirapex ER
	Ropinirole Extended-Release (non-ergot)	Requip XL
MAO Inhibitors	Selegiline (MAO-B selective)	Deprenyl, Eldepryl
	Rasagiline (MAO-B selective)	Azilect
	Zydis selegiline (MAO-B selective	Zelapar
	Safinamide	Xadago
COMT Inhibitors	Entacapone	Comtan, Stalevo (with CD/LD)
	Tolcapone	Tasmar
Antivirals	Amantadine	Symmetrel
Anticholinergics	Trihexyphenidyl	Artane
	Benztropine	Cogentin
	Procyclidine	Kemadrine
	Biperiden	Akineton

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3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Original NDA Submission

The sponsor (Kyowa Pharmaceutical, Inc. submitted a new drug application (NDA) dated March 29, 2007, and received April 25, 2007, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (istradefylline) tablets (b) (4) 20mg, and 40mg.

The Agency was unable to conclude substantial efficacy of istradefylline after NDA review of the original submission.

The following quotations were abstracted from reviews by the clinical team (Drs. Katz, Temple, Hershkowitz, Podskalny) and by the statistical team (Drs. Siddiqui, Jin, Mahjoob) and outline key concerns about substantial efficacy of istradefylline:

- Dr. Katz (DNP Division Director): "However, these results taken as a whole also very strongly suggest that the finding is relatively unstable; that is the drug effect is quite weak."

- Dr. Temple (ODE 1 Office Director): "I agree with Dr. Katz's conclusion that this lack of a broader effect, not seen with other drugs makes istradefylline non-approvable at this time."

- Dr. Hershkowitz (Clinical Team Leader): :It is presently difficult to conclusively determine efficacy because of the following: 1) The large number of contradictory negative studies, 2) the relatively small therapeutic effect, 3) the relatively shallow dose response and exposure response relation, 4) the almost complete lack of statistical significance observed in secondary endpoints, including those that will allow a determination of a significant clinical effect (e.g. CGI and PGI), 5) the absence of a statistically significant effect in a monotherapy trial in early Parkinson's."

- Dr. Podskalny (Primary Clinical Reviewer): "Considering the entire body of clinical trials evidence, istradefylline does not demonstrate consistent superiority compared to placebo in subjects with advanced Parkinson's disease at 10 mg, 20 mg or 40 mg/day." "The opinion of this reviewer is that istradefylline does not meet the agency standards for proving efficacy and it should not be approved for marketing as an adjunctive medication for the treatment of Parkinson's disease in the United States."

- Statistical Team (Drs. Siddiqui, Jin, Mahjoob): "Among the remaining three studies, it was found that istradefylline 20 mg, 40 mg, and 60mg were efficacious (but the evidence of efficacy was not strong) in reduction from Baseline to Endpoint in Percentage of Awake Time Per Day Spent in the OFF State--protocol specified primary measure (Table 5). The istradefylline 20 mg dose was not statistically significant in studies #6002-US-006 and #6002-US-013 in reducing the total awake time per day spent in an OFF state (secondary

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measure). The other secondary efficacy measures including the UPDRS I to IV total scores at study endpoint and CGI-I / PCGI-I scores also failed to demonstrate the efficacy of the istradefylline 20mg, 40mg, and 60mg doses across the three studies. So, the overall efficacy of istradefylline was uncertain."

Non-Approvable Letter

A non-approvable letter was issued on 2/25/08. An abstract of the key information communicated this letter is shown below here.

"CLINICAL
We acknowledge that you have submitted three well-controlled studies (Studies 005, 006, and 013) that show effectiveness for the adjunctive use of istradefylline 20mg, 40mg, and 60mg/day (without clear evidence of dose response) in decreasing the percent of time awake spent in the OFF state in patients with advanced Parkinson's Disease (PD). Several other well-controlled studies of adequate size, however, do not show such an effect and in one of those studies, Study EU-007, an active control, entacapone, gave an almost significant result (p=0.06) while istradefylline showed essentially no effect. Entacapone, moreover, had a favorable effect on the PGI, a patient-rated global measure in that study, while istradefylline did not. These findings, taken together, establish effectiveness in decreasing OFF time, but raise questions about the strength of the finding.

A more important problem, raising the critical question of what patients should receive istradefylline, is raised by the uniform failure of the trials to find any other result that supports the clinical utility of istradefylline or suggests meaningful benefit to patients. There are no nominally significant between treatment contrasts favoring istradefylline compared to placebo on any secondary outcomes in any of the trials, including those assessing other symptoms of PD (e.g., UPDRS, ON time) or global measures of functioning (e.g., CGI, SF-36). These results are conspicuous, compared to all other recently approved treatments for advanced PD, for the absolute lack of demonstrable effect on these other measures. We acknowledge that there is no requirement under law that a new drug be as good as other available treatments, but any inferiority should not represent a risk to patients. It could perhaps be argued that these other treatments provide only symptomatic benefits, and that, substituting an "inferior" treatment would pose no important harm to patients, but we do not agree with this view. Parkinson's Disease is a serious disease, and effective symptomatic treatment can prevent serious clinical outcomes (e.g., falls), even if the treatment has no effect on the underlying progression of the illness, and inferior performance with respect to these other endpoints represents real risk. Although we recognize that the comparative observation that all other recently approved treatments for advanced PD show advantages compared to placebo on signs and symptoms other than OFF time whereas yours does not is based on cross-study comparisons, which are typically unreliable, in this case, we believe that the totality of the evidence justifies our concerns. In addition, in Study EU-007, the one study that included an active comparator (entacapone), entacapone showed an effect on the PGI, while istradefylline did not. Admittedly, of course, this was a study that showed no effect of istradefylline on OFF time. The lack of effect on the disease is further supported by the lack of a statistically significant change in UPDRS, CGS, and PGI

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scores in the double-blind, placebo controlled study (Study 051) examining istradefylline 40mg as monotherapy in Parkinson's disease.

It is possible, we suppose, that this class of compounds, in contrast to dopaminergic agents, has a very specific effect in patients with PD, and improves OFF time with no effect on any other PD symptoms, but this does not help identify a population that should be given istradefylline, rather than other available treatments that improve not only OFF time, but other symptoms as well. Further, even if this "specific-effect" hypothesis were somehow true, we would still expect that any important effects on OFF time would translate into an improvement on non-specific global and/or quality of life measures, especially those measures that are rated by patients. The complete lack of such improvement across multiple studies and measures suggests either that the effect seen on OFF time is inconsistent or clinically trivial, and/or that some effects of the drug are sufficiently distressing to cause patients' overall judgments to be that no benefit was obtained.

These data, then, taken as a whole, lead us to conclude that there appears to be no population for whom istradefylline would be a suitable choice, and, therefore, we cannot support its approval at this time. However, we do believe that it might be possible that, with additional data, approval of the application could be supported.

Specifically, if you were to demonstrate, in an adequately designed and conducted controlled trial, that patients with advanced PD, who had been explicitly maximally and optimally treated with all appropriate available treatments, had a decrease in OFF time on istradefylline compared to placebo, this might support approval of the application, as the gain in OFF time would not be obtained at the expense of other benefits. We, of course, would be happy to work with you to design such a study."

Meeting Following Non-Approvable Letter

A post-action meeting was held between the sponsor and the Agency on 4/7/08 to discuss the non-approvable letter and a path forward for the sponsor. The sponsor made various post-hoc arguments and discussed additional analyses about the efficacy of istradefylline. The following quotes abstracted from the meeting minutes (4/17/08) illustrate important views, perspectives, and recommendations of the Agency for the sponsor. Yellow highlight has been added below here by this reviewer for emphasis of certain sections.

"Meeting Discussion Comments:

- **While the pivotal trials conducted in support of this application demonstrated a small effect on the primary outcome variable, a decrease in " percent of awake OFF" time, Istradefylline's beneficial effect compared to placebo on the primary outcome variable was not consistent in the pivotal clinical trials. A second problem is that there was an absence of any positive effects on important secondary outcome variables such as the investigator and subject rated global measures, quality of life measures and the UPDRS part III subscales. The lack of efficacy on any other outcome measure makes it difficult to identify the target population best suited to receive this treatment. This is**

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a very unusual outcome for a Parkinson's drug because currently approved products also demonstrate improvements on other secondary outcomes, in addition to decreasing OFF time. This leads to the conclusion that the only effect associated with istradefylline is a small reduction in OFF time.

- **Virtually every other medication approved for the symptomatic treatment of Parkinson's disease (PD) not only improves OFF time but they also improve key secondary outcome measures describing improvement in functional ability or symptom management. If istradefylline were prescribed lieu of other agents to patients with advanced PD as an alternative to one of these medications, patients will run the risk of adverse consequences (e. g., falls) because symptoms of PD other than OFF time would not be adequately treated, as they would be if a different drug were taken. Reducing OFF time alone is still desirable in patients with advanced PD but only after medical management reached a plateau with respect to these important secondary clinical outcomes. In the scenario of a maximally treated patient, where no additional gains in quality of life, global improvement and motor function could be achieved with approved medical therapy, an isolated improvement in OFF time would be a benefit over their current PD treatment.**

- **The most likely path forward in the development of istradefylline is to conduct another study. The design of this study should target a Parkinson's population that is confirmed to be maximally or optimally treated with a combination of currently approved Parkinson's drugs. Adding istradefylline to maximally treated Parkinson's patients and demonstrating a consistent effect on reducing OFF time compared to placebo would be considered a benefit. Data documenting subjects enrolled in the completed trials were maximally treated is absent from the current application.**

- **The Division thinks that conducting a new study is the best way forward; however, the Division is open to an argument, supported by data, that adequately reflects efficacy in maximally treated patients. However, by study design the division believes that patients were not optimally/maximally treated.**

- **The sponsor inquired about the definition of optimally/maximally treated, and was told that there is no definitive definition, but the elements of maximal treatment would take into consideration the type of drug, the number of drugs administered, the duration of adjustment and maintenance of optimal treatment, and the clinical response (efficacy vs side effects). The Division recommended that the sponsor consult with Parkinson's experts for developing a clinical definition of optimally/maximally treated patients and in designing a study that would achieve this goal.**

- **Kyowa's representatives described a nearly completed study of approximately 300 subjects treated with istradefylline, which was conducted exclusively in Japan. The sponsor hopes this study will provide additional data to support the efficacy of istradefylline in advanced PD. The sponsor was reminded that a large clinical trial**

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experience was documented in the NDA application that essentially failed to consistently demonstrate the efficacy of istradefylline on secondary outcomes, and the review of future efficacy claims for Parkinson's disease would include considerations of this experience. Whether or not the results of the ongoing Japanese study would alter the division's opinion regarding the efficacy of istradefylline in advanced PD, is a matter of review. The results of this nearly completed trial would have to be compelling in favor of istradefylline in light of the inconsistent effects reported in the previous clinical trials. There would have to be an adequate explanation as to why this study results differ from others. Furthermore, even if the study effect is robust and there is an explanation for the difference with other studies, the division would be concerned that this is a wholly foreign study. The division advises the Sponsor to perform the study described above.

The recommended process forward is:

1. **The sponsor will submit a complete protocol, not a draft of synopsis, to the Division as a special protocol, which would start a 45-day review clock. The special protocol should take into consideration the requirements for optimal treatment, treatment duration, and the drugs administered.**

2. **The division will provide comments to the sponsor as soon as possible after the review is completed.**

3. **After the protocol design has been agreed upon, the sponsor should conduct the study. It is recommended that the phase 4 Clinical Pharmacology study, that is referenced in the action letter, be performed as well, rather than wait for approval and conduct the study as a Phase 4 commitment.**

4. **The sponsor should respond to the action letter, by including the clinical study reports for the agreed upon special protocol and the Clinical Pharmacology study, and the complete requested nonclinical information.**

- **The sponsor inquired about the possible advantage of a new class of drugs, and was informed that, in general, there is no assumption that a new class of agent is better. The division feels that if the Sponsor believes this is the case it is incumbent on them to prove it empirically."**

<u>Meeting (12/2/12) Planning New Pivotal Study to Address Agency/DNP Concerns</u>

A meeting between the sponsor and the Agency/DNP was held on 12/2/12 to discuss the best way to support an NDA resubmission and plan for a new pivotal trial. The following information informing the sponsor what additional efficacy was needed by the Agency to support an NDA

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resubmission was abstracted from meeting minutes (1/4/13). Yellow highlight has been added below here by this reviewer for emphasis of certain sections.

"Question 1:
In the February 25, 2008 Action Letter FDA stated that they would consider the outcome of one additional study in a specified Parkinson's disease population in support of an approval for istradefylline. Please can FDA confirm that this approach is still acceptable?

Preliminary FDA Response: ***(Editorial note: Line #8 "400 mg of levodopa, at least at 4 times per day" was corrected to read "400 mg of levodopa per day")***

Although one additional study may help support approval of an NDA for istradefylline, it remains a review issue. The population studied and the robustness of results are important factors we will consider during our review of the NDA.

In our action letter and during the Post-NDA Review meeting (4/7/08), we recommended that you conduct an additional trial in patients who are maximally treated with the available medications for advanced Parkinson's disease. Your current protocol does not target this population. Instead, patients entering the trial are only required to take 400 mg of levodopa per day. The inclusion criteria do not require patients to have persistent motor disability despite treatment with recommended dosages of other drugs indicated for the treatment Parkinson's disease or documentation that these patients did not tolerated clinically effective doses of these medications. The population that you plan to study is typical for drugs seeking approval for patients with advanced-stage Parkinson's disease. However, a "maximally treated" population is different from patients you have studied in the five completed trials included in your NDA and the more recently completed Japanese trials.

Results from a trial of patients with advanced Parkinson's disease who are not maximally treated would need to be "robust" and statistically significant for the primary efficacy endpoint and on many of the secondary efficacy endpoints. A second possible scenario is to demonstrate effectiveness in patients who are maximally treated (based specifically on defined and agreed on upon criteria). Sensitivity analyses should also indicate that the treatment benefit is robust. The following is an example of inclusion criteria (but not the only) that may help define a patient with "maximally treated" advanced Parkinson's disease:

- **The patient is taking a minimum daily dose of levodopa of 600 mg or higher.**
- **The patient also taking at least one or more other classes of drugs (i.e., dopaminergic agonist, catechol ortho methyl transferase-COMT inhibitor, and/or monoamine oxidase-MAO-B inhibitor) for Parkinson's Disease besides levodopa/carbidopa.**
- **The patient is experiencing persistent motor disability, despite concurrent**

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treatment with multiple drug classes (dopaminergic agonist, COMT inhibitor, and/or MAO-B inhibitor) when such drugs were used at a minimum clinically effective dose (e.g., a percentage of the maximally recommended doses). Each adjunctive medication(s) must be used for a sufficient period to reach pharmacokinetic steady state.

- **The patient has documented intolerance to a class of antiparkinsonian drugs such as a dopamine agonist, COMT inhibitor or MAO-B inhibitor. We believe that it is possible to develop inclusion criteria that provide reasonable evidence that patients with advanced Parkinson's disease are maximally treated with available drugs.**

The decision of whether to study istradefylline in a population that is maximally treated with other drugs or study a typical population of patients with advanced-stage Parkinson's disease (as your currently propose), is yours. However, the results of a trial performed in patients with advanced Parkinson's disease, who are not "maximally treated", must demonstrate a robust effects (benefit) on the primary and important secondary endpoints in order to address the concerns about istradefylline described in the Not Approvable letter.

Meeting Discussion:

- *The Sponsor agreed with the Agency's recommendation to develop criteria that will select patients for the proposed Phase 3 trial who are "optimally" treated, with medications approved for the treatment of Parkinson's disease. However, the sponsor did not agree with the Agency's recommended inclusion criteria requiring patients take at least 600 mg levodopa daily. The Sponsor noted that patients could be "optimally" treated with approved drugs for the treatment of Parkinson's disease but still not require 600 mg or more of daily levodopa. The Sponsor believes patients taking 600 mg of levodopa a day might be candidates for deep brain stimulation (DBS). The Agency noted that taking 600 mg per day of oral levodopa, or more, is not by itself an indication for requiring DBS. The Agency noted that the 600 mg total daily levodopa dose criterion is not an absolute requirement. If the proposed trial is designed to demonstrate istradefylline is effective in "optimally/maximally" treated patients with advanced Parkinson's disease but who are still experiencing fluctuations (significant off time), the Sponsor must include well defined inclusion criteria to ensure patients entering the trial are "optimally" treated with available medications."*

3.2. Summary of Presubmission/Submission Regulatory Activity

A face-to-face Pre-NDA meeting between the sponsor and Agency was held on 2/15/18 to plan details of the NDA resubmission. The Agency/Division of Neurology Products (DNP) discussed with the sponsor details regarding the planned resubmission. The main method for statistical analyses in the Integrated Summary of Efficacy (ISE) was Mixed Model Repeat Measures (MMRM).

The resubmission of this NDA would consist of results from three new pivotal trials (0608, 009,

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and 014) which were not contained in the original submission. Studies 0608 and 009, which had been conducted in Japan, were "old" studies completed (by 2011) after issuance of the Non-Approvable but prior to the 2012 meeting with the sponsor planning the new pivotal trial (014) attempting to address FDA concerns about showing efficacy in a different population of patients.

3.3. Foreign Regulatory Actions and Marketing History

Istradefylline was approved in Japan (with the brand name NOURIAST) in March 2013 with the indication of improvement of wearing-off phenomena in patients with Parkinson's disease on concomitant treatment with levodopa-containing products.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The following is an abstracted overall assessment of findings and recommendations from the most recent review:

"The clinical sites of Drs. Okamoto, Toda, and Yokochi were inspected in support of this NDA. These inspections covered Protocols 6002-0608 and 6002-009. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

This Clinical Inspection Summary is based on communications with the field investigator. Establishment Inspection Reports (EIRs) have not been received from the field and are pending final review. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

At one of the sites (Toda), the clinical investigator did not report a fall occurring in one subject since this subject had a medical history of a "propensity to fall" and the clinical investigator did not consider this event as a worsening of the propensity to fall. However, on face, it would be difficult to make such a determination. If the review division is interested in evaluating the overall occurrence of falls during this study, you may wish to consider asking the sponsor to provide this information.

Reviewer Comment(s)

The OSI inspections did not identify any significant problems or concerns for the 3 Japanese sites which were inspected.

4.2. Product Quality

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I am not aware of any concerns about Product Quality (refer to Product Quality reviews).

4.3. Clinical Microbiology No significant

Not Applicable (NA)

4.4. Nonclinical Pharmacology/Toxicology

NA

4.5. Clinical Pharmacology

The Clinical Pharmacology team (Dr. Gopichand Gottipati was the primary reviewer) concluded that there was dose proportionality for istradefylline exposure and that there was no exposure response for istradefylline. The team also conducted pharmacokinetic (PK) exposure analyses based upon the weight subgroups assessed for efficacy and found that exposure did not decrease as weight increased.

The Clinical Pharmacology Team had the following recommendations for dosing:

General dosing instructions:
The recommended doses are either 20 mg or 40 mg administered orally once daily, with or without food.

Dosing in patient subgroups (intrinsic and extrinsic factors):

- No dose-adjustment is needed in patients with mild hepatic impairment (Child Pugh A).
- Limit NOURIANZ dose to 20 mg once daily in patients with moderate hepatic impairment (Child-Pugh B). Closely monitor patients with moderate hepatic impairment for adverse events when on NOURIANZ treatment.
- Avoid use in patients with severe hepatic impairment (Child-Pugh C).
- No dose adjustment is needed in patients with mild, moderate or severe renal impairment. NOURIANZ was not studied in patients with end stage renal disease (ESRD) or in ESRD requiring dialysis.
- Limit NOURIANZ dose to 20 mg once daily when used concomitantly with strong CYP3A4 inhibitors.
- Avoid use with strong CYP3A4 inducers.
- Smoking can reduce exposure to NOURIANZ. In patients who smoke 20 or more cigarettes per day, the recommended NOURIANZ dose is 40 mg once daily.
- NOURIANZ is an inhibitor of 3A4 and p-gp, therefore sensitive 3A4 and p-gp substrates may need to be closely monitored for adverse events.

4.6. Devices and Companion Diagnostic Issues

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NA

4.7. Consumer Study Reviews

NA

4.8. Statistics

Dr. Xiang Ling is the primary statistical reviewer for this NDA. Although she presented results for all 3 new, pivotal trials (0608, 009, 014) which were submitted, her review focused only on the two Japanese trials (0608, 009) and the primary efficacy endpoint (change from baseline in total OFF time). The only information presented from Study 014 was a brief outline about the study and the results for the primary efficacy endpoints. Her review concluded that there was evidence to support istradefylline efficacy based solely upon the two Japanese trials.

Reviewer Comment(s)

- The statistical review did not address nor discuss any previous efficacy results from the original submission nor the previous statistical review but simply noted that the original submission received a Non-Approvable letter.

- Although Dr. Ling's review described secondary efficacy variables which had been outlined in the protocol, there was no presentation or discussion of results of secondary efficacy endpoints (including what I consider the most important efficacy endpoint: change from baseline for ON time without troublesome dyskinesia) in the new trials. Dr. Ling has considered the secondary efficacy variables (i.e., endpoints) which had been described in the protocols and Statistical Analysis Plans (SAPs) as "exploratory" because a statistical plan/procedure had not been specified for adjusting multiplicity. However, I note that the original statistical review (by Dr. Siddiqui, Primary Reviewer) discussed results of secondary efficacy variables and did not call them "exploratory" despite the fact that a plan/procedure had not been specified for adjusting for multiplicity in the pivotal trials reviewed in the original submission. Furthermore, all clinical reviews (by Drs. Podskalny, Hershkowitz, Katz, Temple) in the original review discussed and/or presented results of secondary efficacy endpoints despite the lack of a statistical plan/procedure for adjusting for multiplicity. In fact, the overall lack of **nominal** statistical significance of many secondary efficacy endpoints was discussed as an important concern contributing to the decision for issuing a Non-Approvable letter and this observation was outlined in that letter as one significant concern/deficiency precluding approval of istradefylline.

  My perspective about analyzing and considering effects on secondary efficacy variables/endpoints differs from that of Dr. Ling. In my experience, many (if not most) FDA statistical reviews for efficacy and my efficacy reviews have presented results of

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secondary efficacy endpoints regardless of the absence of a statistical plan/procedure for adjusting for multiplicity and nominal p values have been presented. The absence of an adjustment for multiplicity regarding multiple secondary efficacy endpoint has always been considered as a recognized limitation in these results and in their interpretation. In my experience, considering efficacy endpoints as exploratory has usually been reserved for endpoints identified in the protocol and SAP as exploratory and not usually for secondary efficacy endpoints without a statistical plan/procedure for adjusting for multiplicity.

- There was no presentation nor discussion of the post hoc weight based subgroup analyses which the sponsor submitted based upon my information request. Subgroup analysis according to weight was conducted and presented by Dr. Ling according to a binary cut-off of < 55 kg vs ≥ 55 kg. Dr. Ling's analysis showed much larger effects on OFF time for both doses in Study 0608 and 40 mg in Study 009 for patients < 55 kg. The treatment effect was smaller for patients < 55 kg for the 20 mg dose in Study 009.

4.9. Clinical Safety

The Safety review was conducted by Dr. Natalie Branagan. Her review did not identify any serious safety concerns for istradefylline. The most common adverse reaction which appeared to be caused by istradefylline was dyskinesia, not an unexpected finding for the population studied.

5. Sources of Clinical Data and Review Strategy

Data and analyses were primarily obtained from the 2/27/19 NDA resubmission at :\\CDSESUB1\evsprod\NDA022075\0047 and subsequent information requests submitted by the sponsor during the review. Some data and analyses were obtained from the original NDA submission.

5.1. Table of Clinical Studies

Table 9 is a listing of all 8 clinical pivotal trials assessing placebo-controlled efficacy and safety of istradefylline.

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Table 9 Tabular Listing of All (8) Istradefylline Clinical Pivotal Efficacy Studies in Patients with Advanced Parkinson's Disease

Protocol No. / CSR Filename	Study Phase	Study Population[a]	Total Subjects Randomized	Study Design	Treatment Duration	Dose	Pre-specified Primary Efficacy Endpoint Change from baseline to endpoint in:
Randomized, Placebo-controlled Trials							
6002-US-005 6002-US-005-r-en	2b	Treated: 195 Completed: 172 64.0 years (38 to 87 years) M: 117/F: 78	196	Phase 2b, DB, PC, R, parallel-group study to evaluate efficacy and safety in subjects with PD treated with levodopa who experience motor-response complications.	12 weeks	Once-daily oral Tablet: Istradefylline 40 mg/day (1×40 mg) or Placebo	Percentage of awake time/day spent in the OFF state
6002-US-006 6002-US-006-r-en	2b	Treated: 395 Completed: 347 65.0 years (36 to 87 years) M: 264/F: 131	395	Phase 2b, DB, PC, R, parallel-group study to evaluate efficacy and safety in subjects with PD treated with levodopa who experience motor-response complications.	12 weeks	Once-daily oral Tablets: Istradefylline 20 mg/day (1×20 mg + 1 placebo identical to 40 mg) or 60 mg/day (1×20 mg + 1×40 mg) or Placebo	Percentage of awake time/day spent in the OFF
6002-US-013 6002-US-013-r-en	3	Treated: 230: Completed: 207 63.0 years (36 to 87 years) M: 153/ F: 77	231	Phase 3, DB, PC, R, parallel-group study to evaluate efficacy and safety in subjects with PD treated with levodopa who experience motor-response complications.	12 weeks	Once-daily oral Tablet: Istradefylline 20 mg/day (1×20 mg) or Placebo	Percentage of awake time/day spent in the OFF state
6002-0608 6002-0608-r-en	2b	Treated: 362 Completed: 327 65.0 years (37 to 84 years) M: 150/ F: 207	363	Phase 2b, DB, PC, R, parallel-group study to evaluate the efficacy and safety in patients with PD with motor complications treated on levodopa therapy.	12 weeks	Once-daily oral Tablets: Istradefylline 20 mg/day (2×10 mg) or 40 mg/day (2×20 mg) or Placebo	Total hours per day spent in the OFF state

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Protocol No. / CSR Filename	Study Phase	Study Population[a]	Total Subjects Random -ized	Study Design	Treatment Duration	Dose	Pre-specified Primary Efficacy Endpoint Change from baseline to endpoint in:
6002-009 6002-009-r-en-04-14	3	Treated:: 373 Completed :335 67.0 years (33 to 84 years) M: 162/ F: 204	373	Phase 3, DB, PC, R, parallel-group treatment of Subjects with PD with motor complications on levodopa therapy	12 weeks	Once-daily oral Tablets: Istradefylline 20 mg/day (2×10 mg) or 40 mg/day (2×20 mg) or Placebo	Total hours per day spent in the OFF state
6002-US-018 6002-US-018-r-en	3	Treated: 605: Completed: 542 63.0 years (35 to 87 years) M: 403/ F: 202	610	Phase 3, DB, PC, R, parallel-group study to evaluate efficacy and safety in subjects with PD treated with levodopa who experience motor-response complications	12 weeks	Once-daily oral Tablets: Istradefylline 10 mg/day (1×10 mg + 1 placebo identical to 40 mg), or 20 mg/day (1×20 mg + 1 placebo identical to 40 mg), or 40 mg/day (1×40 mg + 1 placebo identical to 20 mg) or Placebo	Percentage of awake time/day spent in the OFF state
6002-EU-007 6002-EU-007-r-en	3	Treated: 464 Completed: 410 62.0 years (34 to 87 years) M: 284/ F: 180	464	Phase 3, DB, PC, R, parallel-group, active-comparator study to evaluate efficacy and safety in subjects with PD treated with levodopa who experience motor-response complications	16 weeks	Once-daily oral Tablets: Istradefylline 40 mg/day (2×20 mg with first levodopa dose + 1 entacapone placebo with subsequent levodopa dose), or Placebo or Entacapone 200 mg with each levodopa dose	Percentage of awake time/day spent in the OFF state
6002-014 6002-014-r-en	3	Treated: 612 Completed: 549 64.0 years (40 to 87 years) M: 375/ F: 237	613	Phase 3, DB, PC, R, parallel-group, to evaluate the efficacy in subjects with moderate to severe PD with motor fluctuations and dyskinesia on levodopa therapy plus at least one additional dopaminergic treatment	12 weeks	Once-daily oral Tablets: Istradefylline 20 mg/day (1×20 mg + 1 placebo identical to 40 mg) or 40 mg/day (1×40 mg + 1 placebo identical to 20 mg) or Placebo	Total hours OFF time/day (Change from baseline to Week 12)

5.2. Review Strategy

This review focuses on efficacy, and the review for safety was conducted by Dr. Natalie Branagan.

A change in percentage of awake OFF time or total OFF time was the primary efficacy endpoint in all 8 pivotal trials. However, a decrease in OFF time (either as OFF hours or % of OFF hours) is not necessarily a therapeutic benefit because a decrease in OFF time can occur due to an increase in ON time with troublesome dyskinesia (not a good therapeutic outcome) and/or due to an increase in sleep time (neither a good therapeutic outcome). Thus, it is critically important and imperative to analyze more specifically and precisely whether a decrease in OFF time reflects a direct therapeutic benefit to the patient such as from an increase in ON time without any dyskinesia or with non-troublesome dyskinesia. This combined outcome (i.e., ON without any dyskinesia + ON with non-troublesome dyskinesia) is referred to as ON time without troublesome dyskinesia and was prospectively planned in the Statistical Analysis Plan (SAP) of 6 pivotal trials (007, 009, 013, 014, 018, 0608). This endpoint was analyzed post-hoc in Studies 005 and 006 after unblinding of data. This efficacy endpoint is always an important corollary endpoint we assess along with the primary efficacy endpoint showing a decrease in OFF time to ensure that the effect is truly beneficial to the patient. In fact, an increase in ON time without troublesome dyskinesia is really the most important outcome one would desire for a drug seeking to demonstrate a therapeutic benefit on ON/OFF time from diaries. Given these facts and this rationale, the DNP has more recently (especially during the last decade) analyzed drugs under NDA review to assess whether a drug showing a decrease in OFF time (either as OFF hours or % of OFF hours) was also associated with a statistically significant increase in ON time without troublesome dyskinesia as the main reason for the decrease in OFF time. The DNP has also recommended to sponsors to consider change from baseline in ON time without troublesome dyskinesia as a primary efficacy endpoint, or at least as the most important, key secondary efficacy endpoint.

In view of this perspective outlined above, my review has focused on determining whether statistically significant changes in the OFF time variable as the primary efficacy endpoint of each pivotal study was also associated with a statistically significant benefit on the corresponding variable ON time without troublesome dyskinesia (i.e. for change of percentage of awake time or of total hours) according the primary, pre-specified statistical analysis. This perspective is important in my determination of whether or not an individual pivotal trial can be considered "positive."

My review focused particularly on assessing the following efficacy perspectives/issues/concerns:

1) assessing a statistically significant effect on the primary efficacy endpoint (in all pivotal trials the primary efficacy endpoint was a diary based change of percentage awake OFF time or total OFF tune (an outcome variable which potentially can suggest a therapeutic

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benefit but which does not necessarily reflect a direct therapeutic benefit) according to the pre-specified primary statistical analysis;

2) assessing a statistically significant therapeutic benefit on ON time without troublesome dyskinesia (a most important diary based outcome measure) for the corresponding outcome (% of awake time or total hours) of the primary efficacy endpoint as a reflection of a direct therapeutic benefit to the patient when a statistically significant effect is observed on an decreasing OFF time variable;

3) assessing the magnitude of the effect on decreasing OFF time and increasing ON time without troublesome dyskinesia to determine whether the decrease in OFF is primarily because of an increase in ON time without troublesome dyskinesia;

4) assessing the robustness of efficacy results relative to a different, desirable statistical analysis (i.e., MMRM) when the primary statistical analysis from many years ago was pre-specified as ANOVA or ANCOVA (with LOCF);

5) assessing statistically significant benefits on other various secondary efficacy endpoints (especially endpoints not related to diary based data such as UPDRS Part II-Activities of Daily Living-ADL, UPDRS Part III-Motor Score, and Global Improvement);

6) assessing whether particular pooled analyses and subgroup analyses of efficacy on ON time without troublesome dyskinesia and OFF time provide important insights into the therapeutic benefit of istradefylline;

7) assessing whether the effects on efficacy observed represent substantial efficacy such that istradefylline would be expected to produce similar efficacy in the U.S. population for whom the treatment is intended.

6. Review of Relevant Individual Trials Which Could Potentially Support Efficacy

6.1. New Individual Pivotal Trials

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- Placebo-Controlled, Double-Blind, Parallel-Group, Fixed Dose Study of KW-6002, Protocol No. 6002-0608 **(Completed 8/5/08)**
- Placebo-Controlled, Double-Blind, Parallel-Group, Confirmatory Comparative Study of KW-6002 in the Treatment of Parkinson's Disease, Protocol No. 6002-009 **(Completed 2/21/11)**
- A Phase 3, 12-week, Double-blind, Placebo-controlled, Randomized, Multicenter Study to Evaluate the Efficacy of Oral Istradefylline 20 and 40 mg/day as Treatment for Subjects with Moderate to Severe Parkinson's Disease, Protocol 6002-014 **(Completed 9/23/16)**

6.1.1. Study Design

Overview and Objective

The objective for showing efficacy was based primarily upon showing a decrease of OFF time either as the percentage of daily awake OFF time or total OFF time.

Trial Design

The trial design of all 8 pivotal studies (005, 006, 007, 009, 013, 014, 018, 0608) was very similar. All trials were double blind, placebo controlled comparing istradefylline in different fixed doses to placebo in Parkinson's patients with motor fluctuations (minimal amount of OFF time). Study 007 also included an active comparator (200 mg entacapone, a COMT inhibitor) to istradefylline 40 mg daily and to placebo. With the exception of study 007 which included treatment over 16 weeks, all other pivotal trials involved treatment over 12 week.

The following describes key features of the study population which had been outlined I the inclusion and exclusion criteria of the respective protocols:

Patients participating in the 8 adequate and well-controlled clinical studies were male or female subjects at least 30 years of age (except in Studies 0608 and 009 where patients had to be at least 20 years of age), diagnosed with idiopathic PD based on the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Diagnostic Criteria and had a Modified Hoehn and Yahr Scale (mH&Y) of stages 2 to 4 when in the OFF state (Studies 005, 006, 013, 0608, 009, 6002-US-018, and 007), and in the ON state (014). Patients were treated with levodopa and a peripheral DOPA-decarboxylase inhibitor (carbidopa or benserazide) and had end-of-dose wearing-off. Patients were to be on a stable regimen of levodopa for at least 4 weeks before randomization into double-blind treatment and to be taking at least 3 or 4 doses. Studies 0608 and 009 required subjects to be taking at least 300 mg/day levodopa. Other antiparkinson medications were allowed. **Patients in 014 were supposed to be "maximally and optimally treated", defined as receiving levodopa ≥ 400 mg/day plus at least one additional dopaminergic Parkinson's disease medication (i.e., dopamine agonist, catechol-O-methyltransferase [COMT] inhibitor, or monoamine oxidase B [MAO-B] inhibitor).**

Patients were required to successfully complete diary training and a practice diary before baseline. After diary training, the required minimum hours/day of OFF time was documented in

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patient-completed 24-hour ON/OFF diaries in the week prior to the baseline visit as shown in Table 10.

Table 10 OFF Time Requirements and Number of Valid Diaries as Inclusion Criterion

Study Number	Average Hours/Day of OFF Time	Number of 24-Hour Diaries to Meet Inclusion Criteria[a]
6002-US-005	2 hours	1-2
6002-US-006	2 hours	1-2
6002-US-013	3 hours	1-2
6002-0608	2 hours	4-7
6002-009	2 hours	4-7
6002-US-018	3 hours	1-2
6002-EU-007	3 hours	1-2
6002-014	2 hours	3

a: Diaries collected during a 7-day period, except for 6002-014 where diaries were collected for three days immediately prior to the Baseline visit.

Study Endpoints

The primary efficacy endpoint in these 3 new pivotal trials (0608, 009, 014) was the change from baseline in the total daily OFF hours based upon diary data. In contrast, the primary efficacy endpoint in the previous 5 pivotal trials (005, 006, 007, 013, 018) was the change from baseline in percentage of daily awake hours OFF.

Additional assessments as secondary efficacy endpoints were based on different assessments of the 24-hour ON/OFF Patient Diary (ON without dyskinesia, ON with dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia, ON without troublesome dyskinesia, asleep), UPDRS, CGI, Patient Global Impression -Improvement (PGI-I) scores, Parkinson's Disease Questionnaire (PDQ), and Medical Outcomes Study 36-item Short Form (SF-36).

Reviewer Comment(s)

- The change from baseline in percentage change of OFF time (while awake or over 24 hours) has been used at FDA as a primary efficacy endpoint for pivotal trials for advanced Parkinson's disease. However, this specific primary efficacy endpoint has been a relatively rare/uncommon primary efficacy endpoint for advanced Parkinson's disease over the last several years. More specifically, I am not aware that over the past many years (e.g., perhaps at least a decade) that this primary efficacy endpoint has been used for approving drugs for treating advanced Parkinson's disease. The change from baseline for total daily OFF hours (an indirect surrogate for therapeutic benefit because a decrease in OFF time might not be beneficial if it was due to increased sleep time and/or increased ON with troublesome dyskinesia) has been a common primary efficacy endpoint accepted in the DNP over the last several years. But it is important to recognize that consideration of efficacy associated with this primary efficacy endpoint also considers

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the importance for demonstrating whether there was also a direct therapeutic benefit to the patient based upon demonstration of a "significant" (i.e.., statistically significant with $p < 0.05$ for treatment difference of drug vs placebo) increase in total daily ON hours without troublesome dyskinesia.

Statistical Analysis Plan

Studies 0608 and 009

The Statistical Analysis Plan (SAP) for studies 0608 and 009 outlined that the primary statistical analysis was to be conducted according to with imputation by last observation carried forward (LOCF).

The following is abstracted from the statistical review by Dr. Ling:

Efficacy Analysis Population
The primary efficacy analysis was conducted on the full analysis set (FAS), consisting of randomized subjects who receive at least one dose of study drug and with at least four valid diary days assessed at any of the post-baseline assessment times.

Analysis of the Primary Endpoint
The primary analysis was carried out using an ANCOVA model, including terms for treatment group and study center, and baseline values as a covariate. Small investigative sites were combined through blinded review before database lock.

The two dose groups were to be compared with placebo using the Williams' test based on the assumption that there is a dose-response relationship. In this procedure, the comparison of istradefylline 40 mg/day versus placebo was tested first at the one-sided 0.025 level of significance. If this test was significant, then the comparison of istradefylline 20 mg/day versus placebo was also performed at the one-sided 0.025 level of significance.

Williams' test statistics were calculated according to the following formula, in which n_P, m_P, n_{20}, m_{20}, n_{40}, and m_{40} represent the numbers of subjects and LS means from the ANCOVA model for the placebo, 20 mg/day KW-6002, and 40 mg/day KW-6002 groups, respectively, and s^2 represents the error variance from the ANCOVA model.

Data Handling Rules
Subjects were to complete ON/OFF diaries on the 7 days prior to each scheduled visit, in which patients record "Asleep," "Off," "On without dyskinesia," "On with non-troublesome dyskinesia," or "On with troublesome dyskinesia" for each 30-minute interval. The total hours spent in the OFF state was defined as the number of 30-minute periods classified as "Off" in the ON/OFF diary multiplied by 0.5 hours, averaged over valid diaries within 7 days before visits. Diaries with less than 5 invalid entries per day (more than one check mark or no check marks in a given 30-minute time period) were considered valid. If less than 4 valid diary days are

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available for evaluation at a particular assessment time, the data for the total hours of awake time per day spent in the OFF state at that assessment time was considered missing.

Handing invalid entries
For the primary analysis, 30-minute periods in patient's diaries with invalid entries will be handled as missing and will not be included in the analysis (observed-case analysis).

A worst-case analysis was specified in the study SAP, in which 30-minute periods with missing entries were substituted with OFF, and those periods with multiple entries were substituted with the worst-case value to be selected from one of the following states in the following order: asleep < ON state without dyskinesia < ON state with non-troublesome dyskinesia < ON state with troublesome dyskinesia < OFF.

Handing missing data for the entire visit
For the primary analysis, if data at Week 12 or Early Termination (ET) were missing, the last-observation-carried-forward (LOCF) approach were used, i.e., the last available post-baseline value was used as the final-evaluation data.

A sensitivity analysis based on repeated-measures model was to be conducted with baseline value as a covariate, fixed effect terms for pooled study site, treatment group, week, and treatment-by-week interaction, and compound symmetry (CS) covariance matrix.

Study 014

The SAP for Study 014 was MMRM which the sponsor adopted based upon DNP recommendations as the best approach for statistical analysis and a better approach than ANCOVA with LOCF. The SAP provided for a hierarchical, sequential analyses of the primary efficacy endpoint for both doses (20 mg, 40 mg) and a key secondary efficacy endpoint (change from baseline for ON time without troublesome dyskinesia) to address multiplicity.

Protocol Amendments

Although there were several protocol amendments for the 3 trials (0608, 009, 014), none seemed to be substantial and meriting presentation or discussion here.

6.1.2. Study Results

Studies 0608 (Japan), 009 (Japan), and 014 (North America/Europe/Israel) which was the study planned with FDA as a Special Protocol Assessment (SPA) and subsequently conducted to address FDA concerns in the non-approvable letter.

Compliance with Good Clinical Practices

Each of the above 3 pivotal trials was supposedly conducted according to Good Clinical

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Practices (GCP).

Financial Disclosure

There were no significant concerns for the financial disclosure based upon the review of the 3 new pivotal studies submitted for review.

Patient Disposition

Study 0608 (Japan)

Table 11 Subject Disposition of Study 0608

Subjects with Informed Consent			423	
Subjects Screened			423	
Screening Failures			60	
Reason for Screening Failures				
Consent Withdrawal			13	
Inclusion Criteria			30	
Exclusion Criteria			21	
Other			0	
		Placebo	20mg/day	40mg/day
Subjects Randomized	n(%)	119(100.0)	119(100.0)	125(100.0)
Subjects Receiving Double Blind Medication	n(%)	119(100.0)	118(99.2)	125(100.0)
Completed [a]				
Week 2	n(%)	117(98.3)	116(97.5)	124(99.2)
Week 4	n(%)	115(96.6)	112(94.1)	122(97.6)
Week 8	n(%)	112(94.1)	107(89.9)	118(94.4)
Week 12	n(%)	109(91.6)	106(89.1)	112(89.6)
Discontinued Prematurely	n(%)	10(8.4)	13(10.9)	13(10.4)
Timing of Discontinuation [b]				
Pre Dose	n(%)	0(0.0)	1(0.8)	0(0.0)
First Dose-<Week 2	n(%)	2(1.7)	2(1.7)	1(0.8)
Week 2-<Week 4	n(%)	2(1.7)	4(3.4)	2(1.6)
Week 4-<Week 8	n(%)	3(2.5)	5(4.2)	4(3.2)
Week 8-<Week 12	n(%)	3(2.5)	1(0.8)	6(4.8)
Reason for Failure to Complete Study Period				
Adverse Event	n(%)	2(1.7)	7(5.9)	8(6.4)
Protocol Violation	n(%)	0(0.0)	0(0.0)	0(0.0)
Non-Compliance	n(%)	0(0.0)	0(0.0)	1(0.8)
Subjects Withdrew Consent	n(%)	7(5.9)	3(2.5)	4(3.2)
Investigator's Decision	n(%)	1(0.8)	3(2.5)	0(0.0)
Other	n(%)	0(0.0)	0(0.0)	0(0.0)

(%): Denominator is randomized subjects for each group.

a) Completed Subjects of Week 2, Week 4, and Week 8 have the treatment duration of 11 days or more, 25 days or more, 53 days or more respectively. Subject who completed 12 weeks means no withdrawal

b) Pre Dose, Subjects did not receive any medication; First Dose to <Week 2, Day 1 to Day 10;
Week 2 to <Week 4, Day 11 to Day 24; Week 4 to <Week 8, Day 25 to Day 52; Week 8 to <Week 12, Discontinuation after Day 53.

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Reviewer Comment(s)

- The vast majority (~ 90 %) of patients randomized to each treatment group completed the trial.

- The most common reason for premature discontinuation associated with istradefylline treatment was adverse event and the incidence was similar (~ 6 %) for the 20 mg and 40 mg dose groups.

Study 009 (Japan)

Table 12 Subject Disposition in Study 009

	Overall	Placebo	KW20 mg/day	KW40 mg/day
Number of subjects screened (consented)	398			
Number of screening failures	25			
Number of subjects by cause of failure (some overlaps):				
Subject's withdrawal request	8			
Failure to meet inclusion criteria	5			
Meeting exclusion criteria	11			
Other	1			
Number of subjects randomized	373 (100%)	126 (100%)	123 (100%)	124 (100%)
Number of subject exposed to IP	373 (100%)	126 (100%)	123 (100%)	124 (100%)
Number of subjects who completed[a]				
Week 2	368 (98.7%)	124 (98.4%)	121 (98.4%)	123 (99.2%)
Week 4	358 (96.0%)	119 (94.4%)	119 (96.7%)	120 (96.8%)
Week 8	342 (91.7%)	112 (88.9%)	113 (91.9%)	117 (94.4%)
Week 12	335 (89.8%)	109 (86.5%)	111 (90.2%)	115 (92.7%)
Number of ETs	38 (10.2%)	17 (13.5%)	12 (9.8%)	9 (7.3%)
Number of ETs by cause:				
TEAE	17 (4.6%)	6 (4.8%)	5 (4.1%)	6 (4.8%)
Protocol violation	1 (0.3%)	1 (0.8%)	0	0
Drug non-compliance	2 (0.5%)	2 (1.6%)	0	0
Subject's withdrawal request	15 (4.0%)	6 (4.8%)	6 (4.9%)	3 (2.4%)
Investigator's discretion	3 (0.8%)	2 (1.6%)	1 (0.8%)	0
Other	0	0	0	0
Subjects by time of withdrawal[b]:				
Pre-dose	0	0	0	0
Weeks 0 to 2	5 (1.3%)	2 (1.6%)	2 (1.6%)	1 (0.8%)
Weeks 2 to 4	10 (2.7%)	5 (4.0%)	2 (1.6%)	3 (2.4%)
Weeks 4 to 8	16 (4.3%)	7 (5.6%)	6 (4.9%)	3 (2.4%)
Weeks 8 to 12	7 (1.9%)	3 (2.4%)	2 (1.6%)	2 (1.6%)

(%): percentage of randomized subjects in each group

a) Subjects who completed 2, 4, or 8 weeks of treatment were exposed to the IP for 11, 25, or 53 days or more, respectively; subjects completing 12 weeks of treatment were those who did not withdraw

b) Pre-dose, subjects received no medication; Weeks 0 to 2, 1 to 10 days of exposure; Weeks 2 to 4, 11 to 24 days of exposure; Weeks 4 to 8, 25 to 52 days of exposure; Weeks 8 to 12, 53 days of exposure and beyond

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Reviewer Comment(s)

- The vast majority (~ 90 %) of patients randomized completed the trial. The incidence of completers was slightly higher progressively in higher istradefylline dose groups compared to placebo.

- Overall, the most common reason for premature discontinuation at the end of the trial (week 12) was adverse event and the incidence for each treatment was essentially similar for all treatment groups.

Study 014 (North America /Europe/Israel)

Table 13 Subject Disposition in Study 014

Status	Placebo (N=204) n (%)	Istradefylline 20 mg/day (N=202) n (%)	Istradefylline 40 mg/day (N=207) n (%)	Total (N=613) n (%)
All Subjects Screened	-	-	-	828
All Subjects Randomized	204 (100.0)	202 (100.0)	207 (100.0)	613 (100.0)
Completed				
Week 2	197 (96.6)	190 (94.1)	199 (96.1)	586 (95.6)
Week 6	191 (93.6)	183 (90.6)	187 (90.3)	561 (91.5)
Week 10	187 (91.7)	181[a] (89.6)	181 (87.4)	549 (89.6)
Completed double-blind period	186 (91.2)	182 (90.1)	178 (86.0)	546 (89.1)
Discontinued prematurely	18 (8.8)	20 (9.9)	29 (14.0)	67 (10.9)
Reason for Discontinuation from Study				
Adverse event	13 (6.4)	10 (5.0)	22 (10.6)	45 (7.3)
Subject withdrew consent	3 (1.5)	7 (3.5)	3 (1.4)	13 (2.1)
Did not meet entry criteria	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
Noncompliance	0	0	2 (1.0)	2 (0.3)
Other[b]	0	2 (1.0)	0	2 (0.3)
Death	0	0	1 (0.5)	1 (0.2)
Prohibited concomitant medication	1 (0.5)	0	0	1 (0.2)

a: One subject missed Visit 10 who subsequently completed the 12-week study.
b: Other reasons include: Subject (b) (6) who was randomized, subsequently found to have failed inclusion criterion #5 (levodopa dose at study entry ≥ 400 mg/day) and was never dosed. Subject (b) (6) who was randomized, dosed for < 2 weeks, only had 1.5 hrs of OFF time during baseline diary review, and did not meet inclusion criterion #11 (an average of at least 2 hrs. of total OFF time at baseline visit).
Source: Table 14.1.2 and Listing 16.2.1.1.

A by-subject listing of disposition is provided in Listing 16.2.1.1. A by-subject listing of screening failures is provided in Listing 16.2.1.2.

Reviewer Comment(s)

- The incidence of premature discontinuation was lowest in the placebo group (~ 9 %) and was slightly higher in the 20 mg istradefylline group (~ 10 %) and dose-dependently higher in the 40 mg istradefylline group (14 %).

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- Although the most common reason for premature discontinuation was adverse event in each treatment group, the incidence for the 40 mg group (~ 11 %) was higher than the incidence for the placebo group (~6 %) or for 20 mg (5 %).

- (week 12) was adverse event and the incidence for each treatment was essentially similar for all treatment groups.

Protocol Violations/Deviations

Not unexpectedly, there were many protocol violations/deviation in all 3 pivotal trials. Overall, protocol violations/deviations were relatively minor and did not appear to have a significant impact on efficacy results and conclusions from efficacy results.

Demographic and Baseline Characteristics (Including Parkinson's disease information)

The following information shows demographic and baseline characteristics particularly for Parkinson's disease.

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Table 14 Demographic and Baseline Characteristics Including Parkinson's disease for Study 0608

Variable	Treatment	Placebo	20mg/day	40mg/day	p-value[a]
	n	118	115	124	
Age (years)	Mean+/-Std Dev	65.0+/-7.6	65.1+/-7.2	63.7+/-8.6	[c]0.417
	Median	65.0	66.0	64.0	
	Minimum, Maximum	38, 84	49, 81	37, 80	
	-<65	57 (48.3%)	49 (42.6%)	64 (51.6%)	[b]0.373
	65-	61 (51.7%)	66 (57.4%)	60 (48.4%)	
Gender	Male	45 (38.1%)	50 (43.5%)	55 (44.4%)	[b]0.574
	Female	73 (61.9%)	65 (56.5%)	69 (55.6%)	
Height (cm)	Mean+/-Std Dev	156.13+/-9.55	157.33+/-8.83	157.87+/-9.11	[c]0.186
	Median	155.00	156.40	157.80	
	Minimum, Maximum	136, 186	136.5, 178	132, 178.2	
Weight (kg)	Mean+/-Std Dev	53.42+/-11.15	54.24+/-10.07	54.97+/-11.25	[c]0.468
	Median	53.25	54.50	55.00	
	Minimum, Maximum	34.6, 84.1	34.7, 85	32, 94.5	
BMI (kg/m^2)	Mean+/-Std Dev	21.82+/-3.55	21.84+/-3.19	21.96+/-3.61	[c]0.984
	Median	21.35	21.70	21.60	
	Minimum, Maximum	14.5, 29.3	15.4, 32.5	13.8, 32.0	
	-<22	64 (54.2%)	59 (51.3%)	70 (56.5%)	[b]0.727
	22-	54 (45.8%)	56 (48.7%)	54 (43.5%)	
Time Since Diagnosis (years)	Mean+/-Std Dev	8.338+/-4.826	8.037+/-4.076	8.089+/-4.048	[c]0.977
	Median	7.770	7.660	7.400	
	Minimum, Maximum	1.06, 30.65	1.41, 18.93	0.39, 21.17	
	-<10	81 (68.6%)	80 (69.6%)	90 (72.6%)	[b]0.781
	10-	37 (31.4%)	35 (30.4%)	34 (27.4%)	
Time Since Onset of Motor Complications (years)	Mean+/-Std Dev	3.506+/-3.015	3.167+/-2.499	3.126+/-2.884	[c]0.555
	Median	2.720	2.690	2.325	
	Minimum, Maximum	0.10, 13.19	0.11, 13.20	0.05, 19.15	
	-<4	82 (69.5%)	75 (65.2%)	86 (69.4%)	[b]0.728
	4-	36 (30.5%)	40 (34.8%)	38 (30.6%)	
Current Smoker	Yes	9 (7.6%)	8 (7.0%)	11 (8.9%)	[b]0.855
	No	109 (92.4%)	107 (93.0%)	113 (91.1%)	
Modified Hoehn and Yahr Scale in the ON State	0	1 (0.8%)	0 (0.0%)	2 (1.6%)	[c]0.376
	1	7 (5.9%)	3 (2.6%)	6 (4.8%)	
	1.5	4 (3.4%)	5 (4.3%)	4 (3.2%)	
	2	46 (39.0%)	41 (35.7%)	47 (37.9%)	
	2.5	29 (24.6%)	28 (24.3%)	33 (26.6%)	
	3	28 (23.7%)	36 (31.3%)	30 (24.2%)	
	4	3 (2.5%)	2 (1.7%)	2 (1.6%)	
	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Mean+/-Std Dev	2.32+/-0.64	2.42+/-0.55	2.31+/-0.63	-
	Median	2.50	2.50	2.50	
	Minimum, Maximum	0.0, 4.0	1.0, 4.0	0.0, 4.0	
Modified Hoehn and Yahr Scale in the OFF State	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	[c]0.395
	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1.5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2	7 (5.9%)	5 (4.3%)	7 (5.6%)	
	2.5	15 (12.7%)	11 (9.6%)	18 (14.5%)	
	3	61 (51.7%)	56 (48.7%)	53 (42.7%)	
	4	35 (29.7%)	43 (37.4%)	46 (37.1%)	
	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Mean+/-Std Dev	3.17+/-0.60	3.28+/-0.60	3.24+/-0.64	-
	Median	3.00	3.00	3.00	
	Minimum, Maximum	2.0, 4.0	2.0, 4.0	2.0, 4.0	

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Table (Continued) Demographic and Baseline Characteristics Including Parkinson's disease for Study 0608

Variable	Treatment	Placebo	20mg/day	40mg/day	p-value[a]
	n	118	115	124	
Total Hours of Awake Time Per Day Spent in the OFF State[d] (h)	Mean+/-Std Dev	6.43+/-2.71	6.79+/-2.86	6.55+/-2.48	[c] 0.598
	Median	6.30	6.60	6.35	
	Minimum, Maximum	2.0, 14.8	2.2, 17.0	2.1, 14.0	
	-<6	54 (45.8%)	47 (40.9%)	51 (41.1%)	[b] 0.693
	6-	64 (54.2%)	68 (59.1%)	73 (58.9%)	
Percentage of Awake Time Per Day Spent in the OFF State[d] (%)	Mean+/-Std Dev	39.50+/-16.13	41.07+/-16.14	39.79+/-15.18	[c] 0.669
	Median	37.40	41.00	38.60	
	Minimum, Maximum	11.4, 90.9	12.6, 92.6	13.6, 90.6	
	-<40	64 (54.2%)	56 (48.7%)	72 (58.1%)	[b] 0.346
	40-	54 (45.8%)	59 (51.3%)	52 (41.9%)	
ON State Without Dyskinesia[d] (h)	Mean+/-Std Dev	7.58+/-3.47	7.79+/-3.48	8.01+/-3.51	[c] 0.606
	Median	8.05	8.30	8.35	
	Minimum, Maximum	0.0, 15.3	0.0, 14.9	0.0, 15.5	
ON State With Dyskinesia[d] (h)	Mean+/-Std Dev	2.19+/-3.20	1.85+/-3.18	1.95+/-3.23	[c] 0.330
	Median	0.05	0.00	0.00	
	Minimum, Maximum	0.0, 13.5	0.0, 12.8	0.0, 15.5	
ON State With Non-Troublesome Dyskinesia[d] (h)	Mean+/-Std Dev	1.52+/-2.40	1.27+/-2.29	1.33+/-2.50	[c] 0.330
	Median	0.00	0.00	0.00	
	Minimum, Maximum	0.0, 10.8	0.0, 12.8	0.0, 15.5	
ON State With Troublesome Dyskinesia[d] (h)	Mean+/-Std Dev	0.67+/-1.46	0.58+/-1.32	0.62+/-1.26	[c] 0.870
	Median	0.00	0.00	0.00	
	Minimum, Maximum	0.0, 8.3	0.0, 6.3	0.0, 5.8	
ON State Without Troublesome Dyskinesia[d] (h)	Mean+/-Std Dev	9.09+/-2.73	9.07+/-2.75	9.34+/-2.80	[c] 0.792
	Median	9.45	9.10	9.25	
	Minimum, Maximum	1.5, 15.3	1.3, 15.0	1.4, 16.5	
Daily Dosage of Prior Levodopa	Mean+/-Std Dev	426.3 ±143.0	407.0 ±113.1	415.3 ±159.2	
	Median	400.0	400.0	400.0	c) 0.726
	Minimum, Maximum	300, 900	300, 700	300, 1500	
	-300	41(34.7%)	40(34.8%)	48(38.7%)	
	300<-600	66(55.9%)	69(60.0%)	68(54.8%)	b) 0.710
	>600-	11(9.3%)	6(5.2%)	8(6.5%)	
Levodopa Mono	Yes	0(0.0%)	0(0.0%)	0(0.0%)	b) -
	No	118(100%)	115(100%)	124(100%)	
DOPAMINE AGONISTS	Yes	105(89.0%)	110(95.7%)	114(91.9%)	b) 0.166
	No	13(11.0%)	5(4.3%)	10(8.1%)	
Combinations of Prior Antiparkinsonian Drugs [e]	Levodopa only	2(1.7%)	1(0.9%)	2(1.6%)	b) 0.982
	Levo+DA	28(23.7%)	27(23.5%)	32(25.8%)	
	Levo+DA+SEL/ENT	38(32.2%)	41(35.7%)	46(37.1%)	
	Levo+DA+SEL/ENT+AMA	25(21.2%)	25(21.7%)	24(19.4%)	
	Others	25(21.2%)	21(18.3%)	20(16.1%)	

a) +:p<0.15, b) Chi-square test, c) Kruskal-Wallis test

d) Concomitant medications except antiparkinsonian drugs that were taken within 4 weeks prior to randomization.

e) DA, dopamine agonists; SEL, selegiline; ENT: entacapone; AMA, amantadine

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Table 15 Demographic and Baseline Characteristics Including Parkinson's disease for Study 009

Characteristic	Treatment Group	Placebo	KW20 mg/day	KW40 mg/day
	Number of Subjects	n = 123	n = 120	n = 123
Age (year)	Mean	65.8	66.1	65.7
	Standard deviation	8.6	8.6	9.0
	Median	66.0	67.0	68.0
	Minimum, Maximum	48, 83	42, 84	33, 82
	< 65	54(43.9%)	48(40.0%)	47(38.2%)
	≥ 65	69(56.1%)	72(60.0%)	76(61.8%)
Gender	M	58(47.2%)	40(33.3%)	64(52.0%)
	F	65(52.8%)	80(66.7%)	59(48.0%)
Height (cm)	Mean	157.86	155.66	158.55
	Standard deviation	10.12	8.67	9.53
	Median	157.60	155.00	158.00
	Minimum, Maximum	138.5, 184.0	125.5, 178.5	139.5, 181.5
Body weight (kg)	Mean	55.55	54.46	56.68
	Standard deviation	12.20	10.96	12.95
	Median	53.20	54.38	56.00
	Minimum, Maximum	35.8, 113.0	32.0, 81.0	34.5, 104.6
BMI (kg/m^2)	Mean	22.17	22.34	22.37
	Standard deviation	3.59	3.40	3.65
	Median	21.70	22.60	22.20
	Minimum, Maximum	15.9, 40.0	15.3, 33.7	14.2, 35.4
	< 22	63(51.2%)	53(44.2%)	57(46.3%)
	≥ 22	60(48.8%)	67(55.8%)	66(53.7%)
History of PD (year)	Mean	7.990	7.301	7.730
	Standard deviation	4.453	4.206	4.547
	Median	7.540	6.375	7.230
	Minimum, Maximum	1.14, 26.02	0.63, 20.02	0.66, 22.80
	< 10	87(70.7%)	90(75.0%)	92(74.8%)
	≥ 10	36(29.3%)	30(25.0%)	31(25.2%)
History of motor complications (year)	Mean	3.432	3.183	3.258
	Standard deviation	3.470	2.759	3.009
	Median	2.500	2.460	2.510
	Minimum, Maximum	0.05, 22.02	0.04, 13.14	0.04, 18.14
	< 4	87(70.7%)	87(72.5%)	89(72.4%)
	≥ 4	36(29.3%)	33(27.5%)	34(27.6%)
Smoking	Yes	8(6.5%)	4(3.3%)	8(6.5%)
	No	115(93.5%)	116(96.7%)	115(93.5%)
Modified Hoehn & Yahr stage (ON)	0	0	2(1.7%)	0
	1	9(7.3%)	6(5.0%)	5(4.1%)
	1.5	2(1.6%)	1(0.8%)	8(6.5%)
	2	41(33.3%)	44(36.7%)	43(35.0%)
	2.5	34(27.6%)	33(27.5%)	30(24.4%)
	3	32(26.0%)	26(21.7%)	32(26.0%)
	4	5(4.1%)	8(6.7%)	5(4.1%)
	5	0	0	0
	Mean	2.4	2.4	2.4
	Standard deviation	0.6	0.7	0.6
	Median	2.5	2.5	2.5
	Minimum, Maximum	1, 4	0, 4	1, 4
Modified Hoehn & Yahr stage (OFF)	0	0	0	0
	1	0	0	0
	1.5	0	0	0
	2	7(5.7%)	9(7.5%)	10(8.1%)
	2.5	16(13.0%)	17(14.2%)	12(9.8%)
	3	52(42.3%)	44(36.7%)	49(39.8%)
	4	48(39.0%)	50(41.7%)	52(42.3%)
	5	0	0	0
	Mean	3.3	3.3	3.3
	Standard deviation	0.6	0.7	0.7
	Median	3.0	3.0	3.0
	Minimum, Maximum	2, 4	2, 4	2, 4

Reference ID: 4482028

Table (Continued) **Demographic and Baseline Characteristics Including Parkinson's disease for Study 009**

Characteristic	Treatment Group	Placebo	KW20 mg/day	KW40 mg/day
Visit 2 ON/OFF diaries	Yes	6(4.9%)	15(12.5%)	7(5.7%)
Re-training	No	117(95.1%)	105(87.5%)	116(94.3%)
Total hours of awake time per day spent in the OFF state (h)	Mean	6.31	6.55	5.97
	Standard deviation	2.47	2.72	2.45
	Median	6.10	6.20	5.80
	Minimum, Maximum	1.9, 13.1	2.0, 14.2	2.0, 13.8
	< 6	58(47.2%)	58(48.3%)	67(54.5%)
	≥ 6	65(52.8%)	62(51.7%)	56(45.5%)
Percentage of awake time per day spent in the OFF state (%)	Mean	38.91	40.59	36.92
	Standard deviation	14.80	16.19	15.10
	Median	37.70	38.65	36.20
	Minimum, Maximum	11.6, 85.3	12.5, 90.8	10.7, 83.7
	< 40	68(55.3%)	63(52.5%)	70(56.9%)
	≥ 40	55(44.7%)	57(47.5%)	53(43.1%)
Total hours of awake time per day spent in the ON state (h) — Without dyskinesia	Mean	8.53	7.93	8.50
	Standard deviation	2.84	3.38	3.54
	Median	8.60	8.35	8.80
	Minimum, Maximum	0.0, 14.5	0.0, 16.0	0.1, 15.6
With dyskinesia	Mean	1.35	1.57	1.83
	Standard deviation	2.50	2.75	3.30
	Median	0.00	0.00	0.00
	Minimum, Maximum	0.0, 11.4	0.0, 11.9	0.0, 12.9
With non-troublesome dyskinesia	Mean	0.94	1.00	1.13
	Standard deviation	1.95	1.71	2.03
	Median	0.00	0.00	0.00
	Minimum, Maximum	0.0, 11.0	0.0, 9.3	0.0, 8.6
With troublesome dyskinesia	Mean	0.41	0.58	0.69
	Standard deviation	1.11	1.63	1.75
	Median	0.00	0.00	0.00
	Minimum, Maximum	0.0, 6.6	0.0, 8.6	0.0, 9.5
Without troublesome dyskinesia	Mean	9.47	8.93	9.64
	Standard deviation	2.54	2.86	2.82
	Median	9.40	9.65	9.60
	Minimum, Maximum	2.3, 14.5	1.1, 16.0	2.2, 15.6
Levodopa dose (mg/day)	Mean	425.4	430.8	420.5
	Standard deviation	146.4	156.5	131.8
	Median	400.0	400.0	400.0
	Min, max	300, 1200	300, 1200	300, 900
	≤ 300	46(37.4%)	47(39.2%)	44(35.8%)
	> 300 but ≤ 600	68(55.3%)	60(50.0%)	69(56.1%)
	> 600	9(7.3%)	13(10.8%)	10(8.1%)
Levodopa alone	Yes	0	0	0
	No	123(100%)	120(100%)	123(100%)
Combination of concomitant antiparkinsonian drugs	Levodopa	2(1.6%)	1(0.8%)	3(2.4%)
	Levodopa + DA	19(15.4%)	15(12.5%)	13(10.6%)
	Levodopa + DA + SEL/ENT/ZNS	49(39.8%)	56(46.7%)	52(42.3%)
	Levodopa + DA + SEL/ENT/ZNS + AMA	33(26.8%)	24(20.0%)	31(25.2%)
	Other	20(16.3%)	24(20.0%)	24(19.5%)

DA: dopamine agonist; SEL: selegiline; ENT: entacapone; ZNS: zonisamide; AMA: amantadine

Reference ID: 4482028

Table 16 Demographic and Baseline Characteristics Including Parkinson's disease for Study 014

Demographic Characteristic	Placebo (N=204)	Istradefylline 20 mg/day (N=201)	Istradefylline 40 mg/day (N=207)	Total (N=612)
Age (years)				
Mean (SD)	63.8 (8.49)	63.5 (8.65)	64.5 (8.17)	63.9 (8.43)
Range (min-max)	41 - 86	41 - 87	40 - 85	40 - 87
Gender n (%)				
Male	124 (60.8)	125 (62.2)	126 (60.9)	375 (61.3)
Female	80 (39.2)	76 (37.8)	81 (39.1)	237 (38.7)
Race, n (%)				
White	199 (97.5)	192 (95.5)	200 (96.6)	591 (96.6)
Asian	1 (0.5)	3 (1.5)	5 (2.4)	9 (1.5)
Black	2 (1.0)	2 (1.0)	0	4 (0.7)
American Indian or Alaska Native	0	1 (0.5)	0	1 (0.2)
Other	2 (1.0)	3 (1.5)	2 (1.0)	7 (1.1)
Height (cm)				
Mean (SD)	170.0 (9.94)	171.3 (9.78)	170.8 (9.16)	170.7 (9.63)
Range (min - max)	143 - 208	137 - 193	140 - 193	137 - 208
Weight[a] (kg)				
Mean (SD)	78.3 (15.65)	80.9 (16.35)	78.7 (16.97)	79.3 (16.35)
Range (min - max)	46 - 144	49 - 135	44 - 140	44 - 144
Current Smoker, n (%)				
Yes	5 (2.5)	12 (6.0)	9 (4.3)	26 (4.2)
No	199 (97.5)	189 (94.0)	198 (95.7)	586 (95.8)
Number of cigarettes smoked/day, n (%)				
≤ 5/day	5 (2.5)	12 (6.0)	9 (4.3)	26 (4.2)
Number of cups (8 oz)/day of any caffeinated beverage, n (%)				
Mean (SD)	1.5 (1.37)	1.5 (1.45)[b]	1.4 (1.26)	1.5 (1.36)[c]
Median	1.0	1.0	1.0	1.0
Range (min - max)	0 - 8	0 - 12	0 - 7	0 - 12
Time since diagnosis (years), n (%)				
< 1 year	0	0	0	0
1 - 3 years	7 (3.4)	10 (5.0)	9 (4.3)	26 (4.2)
4 - 7 years	66 (32.4)	76 (37.8)	66 (31.9)	208 (34.0)
≥ 8 years	131 (64.2)	115 (57.2)	132 (63.8)	378 (61.8)
Time since initiation of levodopa (years)				
n	204	201	206	611
Mean (SD)	8.9 (4.03)	8.5 (4.58)	8.9 (4.58)	8.8 (4.40)
Median	8.0	7.0	8.0	8.0
Range (min to max)	2-23	2-24	2-28	2-28

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Table (Continued) **Demographic and Baseline Characteristics Including Parkinson's disease for Study 014**

Characteristic	Placebo (N=204)	Istradefylline 20 mg/day (N=201)	Istradefylline 40 mg/day (N=207)	Total (N=612)
Mean daily levodopa dosage (mg)				
n	204	201	207	612
Mean (SD)	815.02 (385.021)	834.89 (360.769)	841.81 (394.431)	830.61 (380.050)
Median	712.50	775.00	800.00	750.00
Range (min to max)	400.0 - 3150.0	400.0 - 2500.0	300.0 - 2650.0	300.0 - 3150.0
Time since onset of motor complications (years)				
n	203	200	204	607
Mean (SD)	6.1 (4.32)	5.7 (3.98)	6.3 (4.39)	6.0 (4.23)
Median	5.0	4.5	5.0	5.0
Range (min to max)	1-25	1-21	1-22	1-25
Total hours of Awake Time/day spent in the OFF State				
n	204	201	207	612
Mean (SD)	5.41 (2.015)	5.37 (1.975)	5.19 (2.077)	5.32 (2.022)
Median	5.17	5.33	4.83	5.17
Range (min to max)	1.8-14.3	1.0-12.2	1.0-11.0	1.0-14.3
Percentage of Awake Time/day spent in the OFF State				
n	204	201	207	612
Mean (SD)	34.35 (12.252)	33.73 (11.946)	32.96 (12.805)	33.67 (12.337)
Median	32.30	32.93	31.93	32.33
Range (min to max)	10.3-84.4	6.5-82.1	6.2-72.2	6.2-84.4
Total hours of Awake Time/day in the ON State without Troublesome Dyskinesia				
n	204	201	207	612
Mean (SD)	9.25 (2.586)	9.72 (2.305)	9.65 (2.383)	9.54 (2.433)
Median	9.42	9.83	9.67	9.67
Range (min to max)	1.0-14.8	1.8-15.0	1.2-16.0	1.0-16.0
Took any antiparkinsonian medication	204 (100.0)	201 (100.0)	207 (100.0)	612 (100.0)
Levodopa	204 (100.0)	201 (100.0)	207 (100.0)	612 (100.0)
Carbidopa	169 (82.8)	172 (85.6)	184 (88.9)	525 (85.8)
Entacapone	67 (32.8)	71 (35.3)	81 (39.1)	219 (35.8)
Ropinirole hydrochloride	56 (27.5)	47 (23.4)	61 (29.5)	164 (26.8)
Pramipexole dihydrochloride	50 (24.5)	58 (28.9)	44 (21.3)	152 (24.8)
Benserazide	41 (20.1)	46 (22.9)	42 (20.3)	129 (21.1)
Rasagiline mesylate	44 (21.6)	36 (17.9)	46 (22.2)	126 (20.6)
Amantadine hydrochloride	39 (19.1)	25 (12.4)	42 (20.3)	106 (17.3)
Ropinirole	23 (11.3)	28 (13.9)	22 (10.6)	73 (11.9)
Rotigotine	20 (9.8)	20 (10.0)	22 (10.6)	62 (10.1)
Amantadine	19 (9.3)	22 (10.9)	17 (8.2)	58 (9.5)
Rasagiline	17 (8.3)	18 (9.0)	16 (7.7)	51 (8.3)
Selegiline hydrochloride	17 (8.3)	15 (7.5)	11 (5.3)	43 (7.0)
Amantadine sulfate	12 (5.9)	14 (7.0)	14 (6.8)	40 (6.5)
Pramipexole	7 (3.4)	10 (5.0)	11 (5.3)	28 (4.6)

Reviewer Comment(s)

- In each individual pivotal trial (Studies, 0608,009, and 014), demographic and baseline characteristics (including those for Parkinson's disease) were generally similar across treatment groups.

- Overall, demographic and baseline characteristics (including those for Parkinson's disease) in both Japanese trials (Studies, 0608 and 009 appeared to be quite similar. However, there appeared to be some differences worthy of comment for study 014 compared to studies 0608 and 009. Most strikingly, the mean/median weight in studies 0608 and 009 in Japanese patients was near 55 kg but the mean weight across all treatment groups in study 014 was very markedly higher (almost 80 kg). Whereas study 014 enrolled approximately 61 % men to all treatment groups, the Japanese trials enrolled a smaller percentage of men (~ 40-50%) to different treatments. Finally, the mean OFF time at baseline was nearly 1 hour less than the mean OFF time at baseline in both Japanese trials.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other baseline characteristics (particularly related to Parkinson's disease) are presented in the previous section.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There did not appear to be any concerns related to treatment compliance. Concomitant medications (particularly for treating Parkinson's disease) consisting of dopaminergic agonists, Monoamine Oxidase (MAO)- B inhibitors, and/or Catechol-O-Methyltransferase (COMT) inhibitors were used in various combinations with levodopa in the pivotal trials. Rescue medication use did not appear to be a concern.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint for each of the 3 new trials submitted was change from baseline in total OFF hours, probably the most common primary efficacy endpoint for pivotal trials of patients with advanced Parkinson's disease. This primary efficacy endpoint contrasts with the primary efficacy endpoint of the previously submitted 5 pivotal trials. In those trials, the primary efficacy endpoint was change from baseline in percentage of daily OFF time, an endpoint not typically used for pivotal trials in the DNP for more than a decade.

I agree with the statistical reviewer, Dr. Ling, that the vast majority of Hauser diaries were considered valid and that there were relatively few missing or duplicate entries. I also agree with Dr. Ling that the sponsor's sensitivity analyses for OFF time supported the results of the primary analysis of the primary efficacy endpoint for studies 0608 and 009 conducted in Japan.

Study 0608

Reference ID: 4482028

Table 17 shows effect of istradefylline on the primary efficacy endpoint, change from baseline in total daily OFF time.

Table 17 Total House of Awake Time Per Day Spent in the OFF State Based on Patient's ON/OFF Diary – Actual and Change from Baseline Values – Observed Case Analysis – Full Analysis Set Study 0608)

			Placebo n=118		20mg/day n=115		40mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	n	118		115		124	
		Mean	6.43		6.79		6.55	
		Std Dev	2.71		2.86		2.48	
		Minimum	2.0		2.2		2.1	
		Median	6.30		6.60		6.35	
		Maximum	14.8		17.0		14.0	
Endpoint	Statistics	n	118	118	115	115	124	124
		Mean	5.80	-0.62	5.42	-1.36	4.99	-1.55
		Std Dev	3.27	2.17	3.37	2.01	2.68	2.66
		Minimum	0.3	-8.0	0.0	-7.1	0.0	-10.7
		Median	5.55	-0.55	4.70	-1.20	5.10	-1.30
		Maximum	15.8	7.0	14.6	3.0	14.4	5.3
	ANCOVA	LS Mean	5.92	-0.66	5.27	-1.31	5.00	-1.58
		95%C.I.		-1.08, -0.25		-1.73, -0.89		-1.99, -1.17
	ANCOVA (vs. Placebo)	LS Mean				-0.65		-0.92
		95%C.I.				-1.23, -0.07		-1.49, -0.35
		p-value				0.028		0.002
	Williams Test	Test Statistic, DF				2.23, 321		3.22, 321
		p-value				0.013 *		<.001 *

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams' test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-1.1.1 (modified)>

Reviewer Comment(s)

- Each istradefylline dose showed a statistically significant decrease in total OFF time for the primary efficacy endpoint. The mean treatment difference (vs placebo) for change from baseline decrease in OFF time for 40 mg was approximately 40 % higher than the respective decrease for 20 mg.

Study 009

Table 18 shows effects of istradefylline on the primary efficacy endpoint, change from baseline in total daily OFF time.

Reference ID: 4482028

Table 18 **Total Hours of Awake Time Per Day Spent in the OFF State (FAS: observed case) (Study 009)**

			Placebo n = 123		KW20 mg/day n = 120		KW40 mg/day n = 123	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	Number of subjects	123		120		123	
		Mean	6.31		6.55		5.97	
		Standard deviation	2.47		2.72		2.45	
		Minimum	1.9		2.0		2.0	
		Median	6.10		6.20		5.80	
		Maximum	13.1		14.2		13.8	
Final Evaluation	Statistics	Number of Subjects	123	123	120	120	123	123
		Mean	6.03	−0.28	5.46	−1.10	5.00	−0.98
		Standard deviation	3.05	2.32	2.93	1.94	2.84	2.13
		Minimum	0.0	−8.2	0.0	−9.0	0.0	−6.8
		Median	5.90	−0.20	5.60	−1.10	5.00	−1.20
		Maximum	14.8	5.4	14.1	3.8	12.1	5.1
	ANCOVA	LS mean	6.05	−0.23	5.29	−0.99	5.31	−0.96
		95% C.I.		−0.62, 0.16		−1.38, −0.60		−1.35, −0.58
	ANCOVA	LS mean				−0.76		−0.74
	(vs. placebo)	95% C.I.				−1.30, −0.22		−1.27, −0.20
		p-value				0.006		0.008
	Williams test	Test Statistic, DF				2.80, 325		2.76, 325
		p-value				0.003 *		0.003 *

ANCOVA: a model with treatment group as a factor and baseline value and investigative site as covariates
Williams' test p-value*: $p < 0.025$; NS: not significant
Source: Table 14.2-1.1.1

Reviewer Comment(s)

- Each istradefylline dose showed a statistically significant decrease in total OFF time for the primary efficacy endpoint. The mean treatment difference (vs placebo) for change from baseline decrease in OFF time for 20 mg was similar to that of the 40 mg dose indicating no dose-response.

Study 014

The format for presenting efficacy results in the Study 014 final study report was different than that used for the final study reports for both Japanese studies. Whereas the Japanese reports presented tables showing efficacy results for baseline, post-baseline, and change from baseline at week 12 (or final visit), Study 014 presented efficacy results over the whole 12 week treatment period. To present efficacy results for **the primary efficacy endpoint and secondary efficacy endpoints** in a similar fashion as tables for the Japanese studies and also to focus on results at week 12, efficacy results for Study 014 will presented based upon sponsor conducted analyses

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requested by the Division of Neurology Products (DNP) and presented in the Integrated Summary of Efficacy (ISE).

Table 19 shows effect of istradefylline on the primary efficacy endpoint, change from baseline in total daily OFF time.

Table 19 Total Hours per Day in the OFF State at Week 12 - Actual and Change from Baseline - Observed Case Analysis - mITT Analysis Set (Study 014)

Study	Baseline		Post-Baseline		CFB		P Value (Two-sided) (95% CI)	Comment
	n	Mean ± SD	n	LSM ± SD	n	LSM ± SD		
6002-014 (mITT)								
Placebo*	198	5.44 ± 2.005	188	4.48 ± 2.832	188	-0.88 ± 2.186		MMRM/12w[a] **
Ist 20 mg	194	5.40 ± 1.958	179	4.17 ± 2.372	179	-1.20 ± 2.405		
Ist 40 mg*	200	5.23 ± 2.059	176	4.22 ± 2.542	176	-1.15 ± 2.061		
Rx Diff 20mg						-0.32	0.156 (-0.76, 0.12)	
Rx Diff 40mg*						-0.27	0.234 (-0.70, 0.17)	

Reviewer Comment(s)

- Treatment with each dose was associated with a small mean treatment difference (vs placebo) for change from baseline decrease in OFF time but this effect on this primary efficacy endpoint was not statistically significant. The p values for each dose (0.156 for 20 mg and 0.234 for 40 mg) did not even seem close to trending toward statistically significance. These results suggested no efficacy of these istradefylline doses in this population which was primarily composed of Caucasian patients in North America and Europe.

Data Quality and Integrity

Each new pivotal trial (Studies 0608, 009, 014) was conducted according to Good Clinical Practice (GCP) guidelines. There did not appear to be any questions about data quality nor data integrity.

Efficacy Results – Secondary and other relevant endpoints

Statistical significance ($p < 0.05$) is always nominal because whenever a "statistically significant" change was observed, an adjustment for multiplicity had not been made. With the exception of Study 14, which outlined a valid statistical approach addressing multiplicity for a key secondary efficacy endpoint (change from baseline for ON time without troublesome dyskinesia), studies 0608 and 009 (and all 5 pivotal trials in the original NDA submission) did not address multiplicity for analyses of secondary efficacy endpoints.

Study 0608 (Japan)

The following tables show results of many secondary efficacy endpoints based upon diary

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data and other types of assessments.

Table 20 **Total Hours of Awake Time per Day Spent in the ON State without Troublesome Dyskinesia Based on Patient's ON/OFF Diary – Actual and Change from Baseline Values - Observed Case Analysis – Full Analysis Set (Study 0608)**

			Placebo n=118		20mg/day n=115		40mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	n	118		115		124	
		Mean	9.09		9.07		9.34	
		Std Dev	2.73		2.75		2.80	
		Minimum	1.5		1.3		1.4	
		Median	9.45		9.10		9.25	
		Maximum	15.3		15.0		16.5	
Endpoint	Statistics	n	118	118	115	115	124	124
		Mean	9.74	0.65	10.28	1.21	10.59	1.25
		Std Dev	3.37	2.49	3.47	2.36	3.04	2.80
		Minimum	0.0	-7.7	1.6	-5.3	2.0	-5.0
		Median	9.90	0.70	10.30	1.30	10.40	1.00
		Maximum	16.6	8.5	18.0	8.4	19.2	12.8
	ANCOVA	LS Mean	9.81	0.64	10.39	1.21	10.46	1.29
		95%C.I.		0.18, 1.11		0.74, 1.69		0.83, 1.75
	ANCOVA (vs. Placebo)	LS Mean				0.57		0.65
		95%C.I.				-0.08, 1.22		0.01, 1.28
		p-value				0.085		0.048
	Williams Test	Test Statistic, DF				-		2.01, 321
		p-value				-		0.026 NS

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-7.1.1 (modified)>

Reviewer Comment(s)

- Table 20 shows results of istradefylline in Study 0608 on ON time hours without troublesome dyskinesia, an important efficacy endpoint which can indicate a direct therapeutic benefit to patients. High dose 40 mg istradefylline was associated with a p value (0.048) which was barely statistically significant for mean treatment difference (vs placebo) for change from baseline increase in ON time without troublesome dyskinesia. Although the p value (0.085) was trending toward statistical significance for the 20 mg dose, the 20 mg dose did not produce a statistically significant effect on this important endpoint which indicates a clear therapeutic benefit. The mean treatment difference changes were + 0.57 hours for 20 mg and +0.65 hours for 40 mg. This increase (+ 0.57 hours) was similar in magnitude to the treatment difference for decrease in OFF time (- 0.65 hours) for the 20 mg dose. However, the treatment difference for the 40 mg dose for increase (+ 0.65 hours) in ON time without troublesome dyskinesia was somewhat less than the treatment difference for decrease (- 0.92 hours) in OFF time. This apparent discrepancy might suggest the possibility that the difference (0.27 hours) may have been related to an increase in ON time with troublesome dyskinesia and/or an increase in sleep time. Alternatively, precision of diary data collected in 30 minute blocks might have some impact on this apparent discrepancy.

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Table 21 **Total Hours of Awake Time Per Day Spent in the ON State without Dyskinesia Based on Patient's ON/OFF Diary - Actual and Change from Baseline Values - Observed Case Analysis - Full Analysis Set (Study 0608)**

			Placebo n=118		20mg/day n=115		40mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	n	118		115		124	
		Mean	7.58		7.79		8.01	
		Std Dev	3.47		3.48		3.51	
		Minimum	0.0		0.0		0.0	
		Median	8.05		8.30		8.35	
		Maximum	15.3		14.9		15.5	
Endpoint	Statistics	n	118	118	115	115	124	124
		Mean	8.18	0.59	8.93	1.14	9.14	1.13
		Std Dev	4.03	2.63	4.27	2.32	4.13	3.01
		Minimum	0.0	-7.7	0.0	-5.6	0.0	-7.2
		Median	8.70	0.55	9.40	0.90	9.60	1.00
		Maximum	15.9	8.0	18.0	8.4	19.2	12.8
	ANCOVA	LS Mean	8.41	0.61	8.97	1.17	9.00	1.20
		95%C.I.		0.12, 1.10		0.66, 1.67		0.71, 1.68
	ANCOVA (vs. Placebo)	LS Mean				0.56		0.58
		95%C.I.				-0.14, 1.25		-0.09, 1.26
		p-value				0.114		0.091
	Williams Test	Test Statistic, DF				-		1.71, 321
		p-value				-		0.051 NS

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-3.1.1 (modified)>

Reviewer Comment(s)

- Table 21 shows results of istradefylline in Study 0608 on ON time hours without dyskinesia. The mean treatment difference (vs placebo) for change from baseline increase in ON time without dyskinesia was very similar to the increase in ON time without troublesome dyskinesia. This observation suggest that the effect of istradefylline on ON time without troublesome dyskinesia was essentially due to an increase in ON time without dyskinesia.

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Table 22 **Total Hours of Awake Time Per Day Spent in the ON State with Dyskinesia Based on Patient's ON/OFF Diary – Actual and Change from Baseline Values – Observed Case Analysis – Full Analysis Set (Study 0608)**

			Placebo n=118		20 mg/day n=115		40 mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	n	118		115		124	
		Mean	2.19		1.85		1.95	
		Std Dev	3.20		3.18		3.23	
		Minimum	0.0		0.0		0.0	
		Median	0.05		0.00		0.00	
		Maximum	13.5		12.8		15.5	
Endpoint	Statistics	n	118	118	115	115	124	124
		Mean	2.12	-0.08	2.00	0.15	2.28	0.33
		Std Dev	3.33	1.82	3.57	1.57	3.76	2.26
		Minimum	0.0	-5.1	0.0	-6.3	0.0	-5.6
		Median	0.00	0.00	0.00	0.00	0.00	0.00
		Maximum	12.5	9.6	12.7	7.0	16.4	12.9
	ANCOVA	LS Mean	1.91	-0.09	2.14	0.14	2.32	0.32
		95%C.I.		-0.44, 0.27		-0.22, 0.50		-0.03, 0.67
	ANCOVA (vs. Placebo)	LS Mean				0.22		0.41
		95%C.I.				-0.28, 0.72		-0.08, 0.90
		p-value				0.379		0.102
	Williams Test	Test Statistic, DF				-		1.65, 321
		p-value				-		0.058 NS

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-4.1.1 (modified)>

Reviewer Comment(s)

Table 22 shows results of istradefylline in Study 0608 on ON time hours with dyskinesia. Although the mean treatment difference (vs placebo) for change from baseline increase in ON time with dyskinesia was not statistically significant for either dose, the numerical increase for the 40 mg dose was almost twice that of the 20 mg dose.

Reference ID: 4482028

Table 23 **Total Hours of Awake Time per Day Spent in the ON State with Non-Troublesome Dyskinesia Based on Patient's ON/OFF Diary - Actual and Change from Baseline Values – Observed Case Analysis - Full Analysis Set (Study 0608)**

			Placebo n=118		20mg/day n=115		40mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	n	118		115		124	
		Mean	1.52		1.27		1.33	
		Std Dev	2.40		2.29		2.50	
		Minimum	0.0		0.0		0.0	
		Median	0.00		0.00		0.00	
		Maximum	10.8		12.8		15.5	
Endpoint	Statistics	n	118	118	115	115	124	124
		Mean	1.56	0.04	1.34	0.07	1.46	0.13
		Std Dev	2.59	1.66	2.46	1.10	2.68	1.59
		Minimum	0.0	-4.8	0.0	-3.7	0.0	-5.5
		Median	0.00	0.00	0.00	0.00	0.00	0.00
		Maximum	10.3	7.2	12.1	4.4	16.4	6.5
	ANCOVA	LS Mean	1.40	0.02	1.43	0.05	1.44	0.07
		95%C.I.		-0.25, 0.30		-0.22, 0.33		-0.20, 0.33
	ANCOVA (vs. Placebo)	LS Mean				0.03		0.04
		95%C.I.				-0.35, 0.41		-0.33, 0.42
		p-value				0.878		0.825
	Williams Test	Test Statistic, DF				-		0.22, 321
		p-value				-		0.486 NS

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-5.1.1 (modified)>

Reviewer Comment(s)

Table 23 shows results of istradefylline in Study 0608 on ON time hours with non-troublesome dyskinesia. The mean treatment difference (vs placebo) for change from baseline increase in ON time with non-trouble dyskinesia showed a mild decrease for both doses but these changes were not statistically significant.

Reference ID: 4482028

Table 24 **Total Hours of Awake Time Per Day Spent in the ON State with Troublesome Dyskinesia Based on Patient's ON/OFF Diary – Actual and Change from Baseline Values - Observed Case Analysis – Full Analysis Set (Study 0608)**

			Placebo n=118		20mg/day n=115		40mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	n	118		115		124	
		Mean	0.67		0.58		0.62	
		Std Dev	1.46		1.32		1.26	
		Minimum	0.0		0.0		0.0	
		Median	0.00		0.00		0.00	
		Maximum	8.3		6.3		5.8	
Endpoint	Statistics	n	118	118	115	115	124	124
		Mean	0.56	-0.11	0.66	0.08	0.82	0.20
		Std Dev	1.51	0.94	1.74	1.15	1.87	1.33
		Minimum	0.0	-3.5	0.0	-3.9	0.0	-3.4
		Median	0.00	0.00	0.00	0.00	0.00	0.00
		Maximum	8.5	3.7	8.4	6.8	10.7	10.7
	ANCOVA	LS Mean	0.52	-0.10	0.69	0.07	0.87	0.25
		95%C.I.		-0.32, 0.11		-0.15, 0.29		0.03, 0.46
	ANCOVA (vs. Placebo)	LS Mean				0.17		0.35
		95%C.I.				-0.13, 0.47		0.05, 0.64
		p-value				0.262		0.020
	Williams Test	Test Statistic, DF				1.13, 321		2.35, 321
		p-value				0.129 NS		0.011 *

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-6.1.1 (modified)>

Reviewer Comment(s)

Table 24 shows results of istradefylline in Study 0608 on ON time hours with troublesome dyskinesia. The mean treatment difference (vs placebo) for change from baseline increase in ON time with troublesome dyskinesia was twice as great for an increase for the 40 mg dose vs the 20 mg dose. Whereas the increase of approximately 20 minutes of troublesome dyskinesia for the 40 mg dose was statistically significant, the smaller increase for the lower dose was not statistically significant. This effect of the 40 mg dose is not too surprising considering that dyskinesia is the most common adverse reaction of istradefylline and that the increased incidence of dyskinesia is dose-related.

Table 25 **Total Hours Asleep Per Day at Week 12 - Actual and Change from Baseline - Observed Case Analysis - mITT Analysis Set (Study 009)**

6002-0608 (mITT)								
Placebo	118	7.80 ± 1.410	108	7.75 ± 1.643	108	0.11 ± 0.992		MMRM/12w[a]
Ist 20 mg	115	7.57 ± 1.550	106	7.69 ± 1.861	106	0.05 ± 0.918		
Ist 40 mg	124	7.49 ± 1.515	112	7.67 ± 1.563	112	0.03 ± 0.817		
Rx Diff 20mg						-0.06	0.649 (-0.31, 0.19)	
Rx Diff 40mg						-0.07	0.553 (-0.32, 0.17)	
Placebo	118	7.80 ± 1.410	118	7.72 ± 1.636	118	0.10 ± 0.973		ANCOVA/LOCF[b]
Ist 20 mg	115	7.57 ± 1.550	115	7.66 ± 1.823	115	0.04 ± 0.935		
Ist 40 mg	124	7.49 ± 1.515	124	7.68 ± 1.541	124	0.06 ± 0.951		
Rx Diff 20mg						-0.06	0.622 (-0.32, 0.19)	
Rx Diff 40mg						-0.04	0.724 (-0.29, 0.20)	

Reference ID: 4482028

Reviewer Comment(s)

Table 25 shows results of istradefylline in Study 0608 on sleep time. There was no appreciable numerical change for mean treatment difference (vs placebo) for change from baseline in sleep.

Table 26 **Percentage of Awake Time Per Day Spent in the OFF State Based on Patient's ON/OFF Diary - Actual and Change from Baseline Values-Observed Case Analysis - Full Analysis Set (Study 0608)**

			Placebo n=118		20mg/day n=115		40mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	n	118		115		124	
		Mean	39.50		41.07		39.79	
		Std Dev	16.13		16.14		15.18	
		Minimum	11.4		12.6		13.6	
		Median	37.40		41.00		38.60	
		Maximum	90.9		92.6		90.6	
Endpoint	Statistics	n	118	118	115	115	124	124
		Mean	35.74	-3.76	32.85	-8.22	30.35	-9.44
		Std Dev	19.21	13.61	19.69	12.89	16.03	16.11
		Minimum	1.7	-52.0	0.0	-54.1	0.0	-63.1
		Median	33.70	-3.70	29.60	-7.30	32.75	-6.70
		Maximum	85.7	47.4	89.5	15.5	85.7	29.3
	ANCOVA	LS Mean	36.22	-3.88	32.23	-7.88	30.55	-9.55
		95%C.I.		-6.44, -1.32		-10.48, -5.28		-12.07, -7.04
	ANCOVA (vs. Placebo)	LS Mean				-3.99		-5.67
		95%C.I.				-7.57, -0.41		-9.18, -2.17
		p-value				0.029		0.002
	Williams Test	Test Statistic, DF				2.22, 321		3.21, 321
		p-value				0.014 *		<.001 *

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-2.1.1 (modified)>

Reviewer Comment(s)

Table 26 shows results of istradefylline in Study 0608 on percentage of awake time as OFF, the primary efficacy endpoint in all 5 pivotal trials in the original NDA submission. The mean treatment difference (vs placebo) for change from baseline decrease in percentage of awake OFF was statistically significant for both doses and was dose-dependently greater for the higher dose.

Reference ID: 4482028

Table 27 **UPDRS Part II Subscale Score in the ON State - Actual and Change from Baseline Values - Full Analysis Set (Study 0608)**

			Placebo n=118		20 mg/day n=115		40 mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Day -1	Statistics	n	118		115		124	
		Mean	6.4		5.7		6.1	
		Std Dev	5.3		4.6		5.0	
		Minimum	0		0		0	
		Median	6.0		6.0		5.0	
		Maximum	25		24		25	
End-point	Statistics	n	118	118	115	115	124	124
		Mean	5.7	-0.7	5.2	-0.6	5.3	-0.8
		Std Dev	5.2	1.9	4.7	2.4	5.3	2.4
		Minimum	0	-7	0	-12	0	-8
		Median	5.0	0.0	5.0	0.0	4.0	0.0
		Maximum	27	6	26	6	24	9
	ANCOVA	LS Mean	5.5	-0.6	5.5	-0.6	5.4	-0.7
		95%C.I.		-1.0, -0.2		-1.0, -0.2		-1.1, -0.3
	ANCOVA (vs. Placebo)	LS Mean				0.0		-0.2
		95%C.I.				-0.6, 0.5		-0.7, 0.4
		p-value				0.922		0.542
	Williams Test	Test				-		0.62, 321
		Statistic, DF						
		p-value				-		0.322 NS

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-15.1 (modified)>

Reviewer Comment(s)

Table 27 shows results of istradefylline in Study 0608 on UPDRS Part II (Activities of Daily Living-ADL) in ON state. The was no benefit on UPDRS Part II based upon a mean treatment difference (vs placebo) for change from baseline in UPDRS Part II being absent or minimal for either dose.

Table 28 **UPDRS Part III Subscale Score in the ON State - Actual and Change from Baseline Values - Full Analysis Set (Study 0608)**

			Placebo n=118		20 mg/day n=115		40 mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Day -1	Statistics	n	118		115		124	
		Mean	20.6		21.0		21.1	
		Std Dev	9.2		10.6		11.0	
		Minimum	1		2		0	
		Median	21.0		20.0		20.0	
		Maximum	49		61		53	
End-point	Statistics	n	118	118	115	115	124	124
		Mean	16.7	-3.9	14.9	-6.0	15.2	-5.9
		Std Dev	9.4	5.4	10.1	8.3	11.1	6.5
		Minimum	0	-24	0	-46	0	-29
		Median	18.0	-3.0	13.0	-4.0	14.0	-4.0
		Maximum	48	10	63	11	49	7
	ANCOVA	LS Mean	17.2	-3.7	15.2	-5.7	15.2	-5.7
		95%C.I.		-4.8, -2.6		-6.8, -4.6		-6.8, -4.6
	ANCOVA (vs. Placebo)	LS Mean				-2.0		-2.0
		95%C.I.				-3.5, -0.4		-3.5, -0.4
		p-value				0.013		0.012
	Williams Test	Test				2.52, 321		2.56, 321
		Statistic, DF						
		p-value				0.006 *		0.006 *

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-17.1 (modified)>

Reference ID: 4482028

Reviewer Comment(s)

Table 28 shows results of istradefylline in Study 0608 on UPDRS Part III (motor subscale) in ON state. The mean treatment difference (vs placebo) for change from baseline in UPDRS Part III was – 2.0 for each dose. This decrease was nominally statistically significant for both doses.

Table 29 **UPDRS Part IV (Complications of Therapy) A (Dyskinesia) Subscale Score - Actual and Change from Baseline Values - Full Analysis Set**

			Placebo n=118		20 mg/day n=115		40 mg/day n=124	
			Actual	Change	Actual	Change	Actual	Change
Day -1	Statistics	n	118		115		124	
		Mean	1.3		1.1		1.2	
		Std Dev	1.7		1.4		1.6	
		Minimum	0		0		0	
		Median	1.0		1.0		0.0	
		Maximum	8		7		7	
End-point	Statistics	n	118	118	115	115	124	124
		Mean	1.2	-0.1	1.4	0.3	1.2	0.1
		Std Dev	1.6	0.7	1.7	1.1	1.7	1.0
		Minimum	0	-2	0	-2	0	-5
		Median	1.0	0.0	1.0	0.0	0.0	0.0
		Maximum	6	2	8	5	8	4
	ANCOVA	LS Mean	1.1	0.0	1.4	0.3	1.3	0.1
		95%C.I.		-0.2, 0.1		0.1, 0.4		-0.1, 0.3
	ANCOVA (vs. Placebo)	LS Mean				0.3		0.1
		95%C.I.				0.0, 0.5		-0.1, 0.4
		p-value				0.019		0.309
	Williams Test	Test Statistic, DF				-		-1.03, 321
		p-value				-		0.911 NS

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment.
Williams test p-value *: p<0.025, NS: Not Significant <Source: Table 14.2-20.1 (modified)>

Reviewer Comment(s)

Table 28 shows results of istradefylline in Study 0608 on UPDRS Part IV A for dyskinesia complications of therapy. The mean treatment difference (vs placebo) for change from baseline in UPDRS IV A for 20 mg istradefylline showed a statistically significant increase. The smaller change for 40 mg was not statistically significant.

Table 30 **Clinical Global Impression-Improvement (CGI-I) Improvement by Study Visit -Full Analysis Set (Study 0608)**

Visit		Placebo n=118	20mg/day n=115	40mg/day n=124
Endpoint	1.Very much improved	3(2.5%)	1(0.9%)	8(6.5%)
	2.Much improved	14(11.9%)	23(20.0%)	21(16.9%)
	3.Minimally improved	38(32.2%)	41(35.7%)	41(33.1%)
	4.No change	52(44.1%)	45(39.1%)	42(33.9%)
	5.Minimally worse	11(9.3%)	4(3.5%)	11(8.9%)
	6.Much worse	0(0.0%)	1(0.9%)	1(0.8%)
	7.Very much worse	0(0.0%)	0(0.0%)	0(0.0%)
	Total	118(100%)	115(100%)	124(100%)
	Wilcoxon Two-Sample Test (vs. Placebo		z=-1.787 p=0.074	z=1.664 p=0.096
	2.Much improved and above	17(14.4%)	24(20.9%)	29(23.4%)
	3.Minimally improved and above	55(46.6%)	65(56.5%)	70(56.5%)

<Source: Table 14.2-22 (modified)>

Reference ID: 4482028

Reviewer Comment(s)

Table 30 shows results of istradefylline in Study 0608 on the Clinical Global Impression for improvement.. The mean treatment difference (vs placebo) for this scoring was not statistically significant for either dose for indicating overall global improvement with istradefylline treatment.

Study 009 (Japan)

The following tables show results of many secondary efficacy endpoints based upon diary data and other types of assessments.

Table 31 Total Hours of Awake Time Per Day Spent in the ON State without Troublesome Dyskinesia [FAS: observed case] (Study 009)

			Placebo n = 123		KW20 mg/day n = 120		KW40 mg/day n = 123	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	Number of subjects	123		120		123	
		Mean	9.47		8.93		9.64	
		Standard deviation	2.54		2.86		2.82	
		Minimum	2.3		1.1		2.2	
		Median	9.40		9.65		9.60	
		Maximum	14.5		16.0		15.6	
Final evaluation	Statistics	Number of Subjects	123	123	120	120	123	123
		Mean	9.72	0.26	10.10	1.17	10.64	1.01
		Standard deviation	3.00	2.42	3.22	2.52	3.19	2.51
		Minimum	1.3	−6.6	0.0	−9.2	2.8	−6.4
		Median	9.60	0.30	10.45	1.10	10.50	1.00
		Maximum	15.9	7.7	16.6	9.5	18.6	9.3
	ANCOVA	LS mean	9.61	0.26	10.44	1.09	10.42	1.08
		95%C.I.		−0.17, 0.70		0.65, 1.54		0.64, 1.51
	ANCOVA (vs. placebo)	LS mean				0.83		0.81
		95%C.I.				0.22, 1.44		0.21, 1.42
		p-value				0.008		0.008
	Williams test	Test Statistic, DF				2.72, 325		2.70, 325
		p-value				0.003 *		0.004 *

ANCOVA: a model with treatment group as a factor and baseline value and investigative site as covariates
Williams' test p-value*: $p < 0.025$; NS: not significant

Source: Table 14.2-7.1.1

Reviewer Comment(s)

Table 31 shows results of istradefylline in Study 009 on ON time hours without troublesome dyskinesia, an important efficacy endpoint which can indicate a direct benefit to the patient. The mean treatment difference (vs placebo) for change from baseline increase in ON time with without troublesome dyskinesia showed approximately a 0.8 hour statistically significant increase for both doses. This effect was similar in magnitude to the statistically significant decrease in total OFF time hours for each dose and suggested that each decrease in OFF time was due to an increase in ON time without troublesome dyskinesia.

Reference ID: 4482028

Table 32 Total Hours of Awake Time Per Day Spent in the ON State without Dyskinesia [FAS: observed case (Study 009)

			Placebo n = 123		KW20 mg/day n = 120		KW40 mg/day n = 123	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	Number of subjects	123		120		123	
		Mean	8.53		7.93		8.50	
		Standard deviation	2.84		3.38		3.54	
		Minimum	0.0		0.0		0.1	
		Median	8.60		8.35		8.80	
		Maximum	14.5		16.0		15.6	
Final evaluation	Statistics	Number of Subjects	123	123	120	120	123	123
		Mean	8.77	0.24	8.86	0.93	9.35	0.85
		Standard deviation	3.37	2.52	3.86	2.09	4.10	2.70
		Minimum	0.0	−6.5	0.0	−5.6	0.0	−6.4
		Median	8.80	0.30	9.60	0.90	9.90	0.90
		Maximum	15.9	7.7	16.6	7.3	18.6	12.8
	ANCOVA	LS mean	8.60	0.28	9.22	0.90	9.18	0.85
		95%C.I		−0.16, 0.73		0.44, 1.35		0.41, 1.30
	ANCOVA (vs. placebo)	LS mean				0.61		0.57
		95%C.I				−0.01, 1.24		−0.05, 1.19
		p-value				0.054		0.069
	Williams test	Test Statistic, DF				–		1.90, 325
		p-value				–		0.033 NS

ANCOVA: a model with treatment group as a factor and baseline value and investigative site as covariates
Williams' test p-value*: $p < 0.025$; NS: not significant

Source: Table 14.2-3.1.1

Reviewer Comment(s)

Table 32 shows results of istradefylline in Study 009 on ON time hours without dyskinesia. The mean treatment difference (vs placebo) for change from baseline was approximately a 0.6 hour increase for each dose. Although this increase was not statistically significant, each p value was close and trending toward statistical significance. These results suggested that most of the statistically significant increase in ON time without troublesome dyskinesia was likely related to an increase in ON time without any dyskinesia.

Reference ID: 4482028

Table 33 Total Hours of Awake Time Per Day Spent in the ON State with Dyskinesia [FAS: observed case] (Study 009)

			Placebo n = 123		KW20 mg/day n = 120		KW40 mg/day n = 123	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	Number of subjects	123		120		123	
		Mean	1.35		1.57		1.83	
		Standard deviation	2.50		2.75		3.30	
		Minimum	0.0		0.0		0.0	
		Median	0.00		0.00		0.00	
		Maximum	11.4		11.9		12.9	
Final evaluation	Statistics	Number of Subjects	123	123	120	120	123	123
		Mean	1.33	−0.02	1.80	0.23	1.91	0.08
		Standard deviation	2.46	1.58	3.18	1.49	3.52	1.51
		Minimum	0.0	−6.2	0.0	−5.1	0.0	−8.8
		Median	0.00	0.00	0.00	0.00	0.00	0.00
		Maximum	12.1	6.1	15.8	5.3	14.6	6.8
	ANCOVA	LS mean	1.51	−0.08	1.81	0.22	1.68	0.09
		95%C.I.		−0.36, 0.20		−0.06, 0.51		−0.19, 0.37
	ANCOVA	LS mean				0.30		0.17
	(vs.	95%C.I.				−0.09, 0.69		−0.22, 0.56
	placebo)	p-value				0.135		0.390
	Williams test	Test Statistic, DF				-		1.19, 325
		p-value				-		0.139 NS

ANCOVA: a model with treatment group as a factor and baseline value and investigative site as covariates
Williams' test p-value*: $p < 0.025$; NS: not significant

Source: Table 14.2-4.1.1

Reviewer Comment(s)

Table 33 shows results of istradefylline in Study 009 on ON time hours with dyskinesia. The mean treatment differences (vs placebo) for change from baseline in ON time with dyskinesia for both doses showed numerically small increases which were not dose-related nor statistically significant.

Table 34 Total Hours of Awake Time Per Day Spent in the ON State with Non-Troublesome Dyskinesia [FAS: observed case] (Study 009)

			Placebo n = 123		KW20 mg/day n = 120		KW40 mg/day n = 123	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	Number of subjects	123		120		123	
		Mean	0.94		1.00		1.13	
		Standard deviation	1.95		1.71		2.03	
		Minimum	0.0		0.0		0.0	
		Median	0.00		0.00		0.00	
		Maximum	11.0		9.3		8.6	
Final evaluation	Statistics	Number of Subjects	123	123	120	120	123	123
		Mean	0.95	0.01	1.24	0.24	1.29	0.16
		Standard deviation	1.99	1.22	2.30	1.89	2.43	1.09
		Minimum	0.0	−4.2	0.0	−8.7	0.0	−4.5
		Median	0.00	0.00	0.00	0.00	0.00	0.00
		Maximum	11.4	5.9	13.4	9.9	10.0	5.6
	ANCOVA	LS mean	0.98	−0.04	1.27	0.25	1.19	0.16
		95%C.I.		−0.31, 0.22		−0.02, 0.52		−0.10, 0.43
	ANCOVA	LS mean				0.29		0.21
	(vs.	95%C.I.				−0.08, 0.67		−0.16, 0.57
	placebo)	p-value				0.123		0.275
	Williams test	Test Statistic, DF				–		1.34, 325
		p-value				–		0.108 NS

ANCOVA: a model with treatment group as a factor and baseline value and investigative site as covariates
Williams' test p-value*: $p < 0.025$; NS: not significant

Source: Table 14.2-5.1.1

Reference ID: 4482028

Reviewer Comment(s)

Table 34 shows results of istradefylline in Study 009 on ON time hours with non-troublesome dyskinesia. The mean treatment difference (vs placebo) for change from baseline in ON time with troublesome dyskinesia for both dose showed small increases which were not statistically significant.

Table 35 Total Hours of Awake Time Per Day Spent in the ON State with Troublesome Dyskinesia [FAS: observed case] (Study 009)

			Placebo n = 123		KW20 mg/day n = 120		KW40 mg/day n = 123	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	Number of subjects	123		120		123	
		Mean	0.41		0.58		0.69	
		Standard deviation	1.11		1.63		1.75	
		Minimum	0.0		0.0		0.0	
		Median	0.00		0.00		0.00	
		Maximum	6.6		8.6		9.5	
Final evaluation	Statistics	Number of Subjects	123	123	120	120	123	123
		Mean	0.38	−0.03	0.56	−0.01	0.61	−0.08
		Standard deviation	0.95	0.74	1.72	1.48	1.55	0.86
		Minimum	0.0	−3.3	0.0	−6.0	0.0	−5.2
		Median	0.00	0.00	0.00	0.00	0.00	0.00
		Maximum	4.6	3.2	10.9	10.7	7.6	4.0
	ANCOVA	LS mean	0.50	−0.06	0.55	−0.01	0.54	−0.02
		95%C.I.		−0.24, 0.11		−0.19, 0.17		−0.20, 0.16
	ANCOVA (vs. placebo)	LS mean				0.05		0.04
		95%C.I.				−0.20, 0.30		−0.21, 0.29
		p-value				0.683		0.743
	Williams test	Test Statistic, DF				–		0.37, 325
		p-value				–		0.421 NS

ANCOVA: a model with treatment group as a factor and baseline value and investigative site as covariates
Williams' test p-value*: $p < 0.025$; NS: not significant

Source: Table 14.2-6.1.1

Reviewer Comment(s)

Table 35 shows results of istradefylline in Study 009 on ON time hours with troublesome dyskinesia. The mean treatment difference (vs placebo) for change from baseline for both doses did not show an appreciable change.

Table 36 Total Hours Asleep Per Day at Week 12 - Actual and Change from Baseline - Observed Case Analysis - mITT Analysis Set (Study 009)

6002-009 (mITT)								
Placebo	125	7.80 ± 1.580	109	7.87 ± 1.602	109	0.06 ± 0.966		MMRM/12w[a]
Ist 20 mg	121	7.96 ± 1.580	111	7.67 ± 1.831	111	-0.14 ± 1.101		
Ist 40 mg	123	7.71 ± 1.517	115	7.79 ± 1.691	115	-0.02 ± 1.030		
Rx Diff 20mg						-0.20	0.127 (-0.47, 0.06)	
Rx Diff 40mg						-0.08	0.529 (-0.34, 0.18)	
Placebo	125	7.80 ± 1.580	125	7.88 ± 1.718	125	0.06 ± 1.032		ANCOVA/LOCF[b]
Ist 20 mg	121	7.96 ± 1.580	121	7.65 ± 1.833	121	-0.17 ± 1.098		
Ist 40 mg	123	7.71 ± 1.517	123	7.77 ± 1.679	123	-0.05 ± 1.010		
Rx Diff 20mg						-0.22	0.084 (-0.48, 0.03)	
Rx Diff 40mg						-0.10	0.417 (-0.36, 0.15)	

Reviewer Comment(s)

Table 36 shows results of istradefylline in Study 009 on sleep time. The mean treatment difference (vs placebo) for change from baseline in sleep for both doses showed small numerical decreases which were not statistically significant.

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Table 37 Percentage of Awake Time Per Day Spent in the OFF State [FAS: observed case] (Study 009)

			Placebo n = 123		KW20 mg/day n = 120		KW40 mg/day n = 123	
			Actual	Change	Actual	Change	Actual	Change
Baseline	Statistics	Number of subjects	123		120		123	
		Mean	38.91		40.59		36.92	
		Standard deviation	14.80		16.19		15.10	
		Minimum	11.6		12.5		10.7	
		Median	37.70		38.65		36.20	
		Maximum	85.3		90.8		83.7	
Final evaluation	Statistics	Number of Subjects	123	123	120	120	123	123
		Mean	37.13	−1.78	33.54	−7.04	30.85	−6.07
		Standard deviation	18.40	14.13	17.88	12.37	17.38	13.69
		Minimum	0.0	−47.3	0.0	−55.5	0.0	−42.2
		Median	36.40	−1.40	33.85	−6.30	30.90	−5.40
		Maximum	92.2	31.0	87.2	27.7	71.3	31.8
	ANCOVA	LS mean	37.24	−1.55	32.24	−6.55	32.62	−6.17
		95%C.I.		−3.98, 0.88		−9.02, −4.08		−8.59, −3.74
	ANCOVA (vs. placebo)	LS mean				−4.99		−4.61
		95%C.I.				−8.39, −1.60		−7.98, −1.25
		p-value				0.004		0.007
	Williams test	Test Statistic, DF				2.93, 325		2.83, 325
		p-value				0.002 *		0.003 *

ANCOVA: a model with treatment group as a factor and baseline value and investigative site as covariates
Williams' test p-value*: p < 0.025; NS: not significant

Source: Table 14.2-2.1.1

Reviewer Comment(s)

Table 37 shows results of istradefylline in Study 009 on percentage of awake daily OFF time. The mean treatment difference (vs placebo) for change from baseline for percentage of awake daily OFF time for both doses showed similar decreases which were statistically significant.

Table 38 UPDRS part II Subscale Score in the ON State [FAS] (Study 009)

			Placebo n=123		KW20mg/day n=120		KW40mg/day n=123	
			Actual	Change	Actual	Change	Actual	Change
Day -1	Statistics	Number of subjects	123		120		123	
		Mean	5.9		5.3		5.3	
		Standard deviation	5.2		5.2		5.0	
		Minimum	0		0		0	
		Median	5.0		4.0		4.0	
		Maximum	21		29		24	
Final Evaluation	Statistics	Number of subjects	123	123	120	120	123	123
		Mean	5.4	-0.5	4.9	-0.4	4.8	-0.5
		Standard deviation	4.8	1.5	5.5	2.2	4.8	2.0
		Minimum	0	-7	0	-8	0	-8
		Median	5.0	0.0	3.0	0.0	3.0	0.0
		Maximum	21	4	28	11	22	8
	ANCOVA	LS Mean	5.2	-0.3	5.2	-0.3	5.0	-0.5
		95%C.I.		-0.6, 0.0		-0.6, 0.0		-0.8, -0.1
	ANCOVA (vs. Placebo)	LS Mean				0.0		-0.2
		95%C.I.				-0.4, 0.5		-0.6, 0.3
		p-value				0.950		0.489
	Williams Test	Test Statistic, DF				-		0.70, 325
		p-value				-		0.290 NS

LS Mean and p-value are based on the main effects ANCOVA with terms for Baseline, Investigator and treatment
Williams' test p-value*: p<0.025; NS: Not Significant

Source: Table 14.2-15.1

Reviewer Comment(s)

Table 38 shows results of istradefylline in Study 009 on UPDRS Part II (Activities of Daily Living-ADL) in ON state. There was no appreciable mean treatment difference (vs placebo) for change from baseline in UPDRS Part II for either dose.

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Table 39 UPDRS Part III Subscale Score in the ON State [FAS] (Study 009)

			Placebo n = 123		KW20 mg/day n = 120		KW40 mg/day n = 123	
			Actual	Change	Actual	Change	Actual	Change
Day −1	Statistics	Number of Subjects	123		120		123	
		Mean	21.6		21.3		20.7	
		Standard deviation	11.6		10.8		11.0	
		Minimum	1		2		3	
		Median	20.0		21.0		20.0	
		Maximum	58		55		52	
Final evaluation	Statistics	Number of Subjects	123	123	120	120	123	123
		Mean	18.3	−3.2	17.1	−4.2	15.7	−5.1
		Standard deviation	11.1	5.3	11.1	6.0	10.3	6.7
		Minimum	1	−17	1	−22	0	−27
		Median	17.0	−3.0	16.0	−4.0	15.0	−4.0
		Maximum	48	12	54	9	55	10
	ANCOVA	LS mean	18.4	−2.8	17.5	−3.7	16.3	−4.9
		95%C.I.		−3.8, −1.8		−4.7, −2.8		−5.8, −3.9
	ANCOVA (vs. placebo)	LS mean				−0.9		−2.0
		95%C.I.				−2.3, 0.4		−3.4, −0.7
		p-value				0.176		0.003
	Williams test	Test Statistic, DF				1.37, 325		3.04, 325
		p-value				0.086 NS		0.001 *

ANCOVA: a model with treatment group as a factor and baseline value and investigative site as covariates
Williams' test p-value*: p < 0.025; NS: not significant

Source: Table 14.2-17.1

Reviewer Comment(s)

Table 39 shows results of istradefylline in Study 009 on UPDRS Part III (motor subscale) in ON state. The mean treatment difference (vs placebo) for change from baseline in UPDRS Part III decrease was dose-related. Although the smaller decrease for 20 mg was not statistically significant, the much larger decrease for 40 mg was statistically significant.

Table 40 UPDRS Part IV-A (Complications of Therapy – Dyskinesia) at Week 12/16 Actual and Change from Baseline - Observed Case Analysis - mITT

6002-009 (mITT)								
Placebo	125	1.0 ± 1.50	111	1.0 ± 1.23	111	-0.1 ± 0.86		MMRM/12w[a]
Ist 20 mg	121	1.1 ± 1.62	112	1.3 ± 1.98	112	0.2 ± 1.26		
Ist 40 mg	123	1.2 ± 1.70	116	1.1 ± 1.64	116	-0.0 ± 0.75		
Rx Diff 20mg						0.3	0.021 (0.0, 0.6)	
Rx Diff 40mg						0.1	0.611 (-0.2, 0.3)	
Placebo	125	1.0 ± 1.50	125	1.0 ± 1.28	125	-0.1 ± 0.89		ANCOVA/LOCF[b]
Ist 20 mg	121	1.1 ± 1.62	121	1.4 ± 1.92	121	0.2 ± 1.23		
Ist 40 mg	123	1.2 ± 1.70	123	1.1 ± 1.72	123	-0.0 ± 0.82		
Rx Diff 20mg						0.3	0.009 (0.1, 0.6)	
Rx Diff 40mg						0.1	0.443 (-0.1, 0.3)	

Reviewer Comment(s)

Table 40 shows results of istradefylline in Study 009 on UPDRS Part IV A (complications of therapy-dyskinesia). The mean treatment difference (vs placebo) for change from baseline showed a statistically significant increase for the 20 mg dose but the smaller increase for the 40 mg dose was not statistically significant. Of interest, this statistically significant increase in this endpoint for dyskinetic complications of treatment reproduced the exactly same observation in the other Japanese trial (0608) in which the 20 mg dose showed a statistically significant increase on this same endpoint.

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Table 41 Clinical Global Impression-Improvement (CGI-I) Frequencies at Final Evaluation [FAS] (Study009)

	Placebo n = 123	KW20 mg/day n = 120	KW40 mg/day n = 123
1.Very much improved	0(0.0%)	5(4.2%)	3(2.5%)
2.Much improved	13(10.7%)	20(16.7%)	32(26.2%)
3.Minimally improved	32(26.2%)	44(36.7%)	39(32.0%)
4.No change	69(56.6%)	40(33.3%)	42(34.4%)
5.Minimally worse	8(6.6%)	8(6.7%)	5(4.1%)
6.Much worse	0(0.0%)	2(1.7%)	1(0.8%)
7.Very much worse	0(0.0%)	1(0.8%)	0(0.0%)
Total	122(100%)	120(100%)	122(100%)
Wilcoxon two-sample test vs. placebo		z = -2.796 p = 0.005	z = 3.980 p < .001
2. "Much improved" or better	13(10.7%)	25(20.8%)	35(28.7%)
3. "Minimally improved" or better	45(36.9%)	69(57.5%)	74(60.7%)

Source: Table 14.2-22

Reviewer Comment(s)

Table 41 shows results of istradefylline in Study 009 on Clinical Global Impression-Improvement. The mean treatment difference (vs placebo) for improvement based upon this score was statistically significant both doses. These results support the view that each dose resulted in an overall perspective that clinical improvement from treatment was the experience.

Sponsor's View of Generalizability of Foreign Data to the United States Population

The sponsor has summarized information which it believes suggests the generalizability of foreign data (specifically Japanese pivotal trial data) to the U.S. population. The sponsor has noted that the epidemiology, diagnosis, treatment (including guidelines), outcomes of treatment, standard of care, and pharmacokinetics of istradefylline are generally similar with potentially only minimal differences for Japan as for the data outside of Japan (including U.S.). In addition, the sponsor has noted that the study design, demographics, Parkinson's disease history, Parkinson's disease characteristics at baseline, prior and concomitant Parkinson's disease medications, and effect of treatment are similar for the Japanese trials as for the trials outside of Japan (including U.S.).

The following language is an abstracted quotation summarizing the sponsor view of the generalizability of the Japanese data to the U.S. population:

"Although conducted wholly in Japan, a potential limitation discussed by the Agency in earlier communications, the Sponsor believes that studies 6002-0608 and 6002-009 are generalizable to the US population given the similarity in pharmacokinetics, trial designs, entry criteria, conduct characteristics, and methods of analysis. The principles of PD diagnosis, levodopa-based treatment, and treatment of motor fluctuations are all highly similar between the US and Japan. Accordingly, the Sponsor believes the data from all 5 adequate and well controlled studies

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should be considered. The 2 studies (6002-009 and 6002-0608) conducted in Japan further support and replicate the favorable efficacy and safety results observed in the 3 pivotal studies (6002-US-005, 6002-US-006, and 6002-US-013) that included US subjects."

Reviewer Comment(s)

Despite the comments outlined above for the generalizability of the efficacy results of the 2 Japanese trials to all of the results and efficacy outside of Japan, I note that the sponsor has not addressed the following issues/concerns which I consider to be important:

- The DNP wanted to see a demonstration of istradefylline efficacy in a population which had been "optimally" treated and which had been clearly noted in the minutes of the meeting with the sponsor held on 12/2/12 in which the DNP had noted that the results of the 2 Japanese trials did not meet DNP expectations and that additional efficacy was desirable.

- The sponsor did not address the potential that genetic/racial factors for Japanese with patients could have contributed to increased susceptibility to Japanese patients for responding to istradefylline and having much better efficacy response than patients outside of Japan.

- The sponsor did not address that the overall efficacy in the Japanese trials was much greater than efficacy observed outside of Japan for 20 mg and 40 mg doses for the important endpoints of change from baseline in total OFF time and in total ON time without troublesome dyskinesia.

- The sponsor did not address nor provide any possible explanations for the essentially complete lack of efficacy for the 3 pivotal trials (018, 007, 014) , especially in view of the lack of efficacy of the highest 40 mg dose (which the sponsor proposes to market in the U.S.) and which had been comprised primarily of Caucasian patients outside of Japan (and which largely included U.S. patients).

- The inconsistent across efficacy endpoints in studies 006 and 013 (which had been conducted outside of Japan) which had been reviewed in the original NDA submission and had been considered as not supporting efficacy of istradefylline.

- The sponsor's exposure-response analyses did not suggest an effect of weight on exposure-response. However, regarding several post-hoc analyses conducted by the sponsor in response to my information requests for various weight-based analyses of efficacy, the sponsor did not address the significant effects of large weight differences in the Japanese pivotal trials (mean/median weight about 55 kg) vs outside of Japan (mean/median weight 70-80 kg) and the apparent progressive loss of efficacy with increasing weight (and complete loss of efficacy for ON time without troublesome dyskinesia and for OFF time) when weight is $\geq$ 85 kg ($\geq$ 187 lbs). The sponsor simply and generally noted that istradefylline results were typically better than those for placebo without providing any detailed assessments of the many, varied specific analyses related

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to weight.

Study 014

This study planned to enroll patients who had been required to be taking more comprehensive adjunctive treatment than was required previously in all the other 7 pivotal trials. The FDA issued a Special Protocol Assessment (SPA) letter to the sponsor acknowledging FDA's agreement with the design of Study 014.

The following tables show results of many secondary efficacy endpoints based upon diary data and other types of assessments.

Table 42 Actual Total Hours per Day ON Without Troublesome Dyskinesia at Week 12/16 and Change from Baseline - Observed Case Analysis – mITT

Study	Baseline		Post-Baseline		CFB		P Value (Two-sided) (95% CI)	Comment
	n	Mean ± SD	n	LSM ± SD	n	LSM ± SD		
6002-014 (mITT)								
Placebo	198	9.22 ± 2.587	188	10.31 ± 3.376	188	0.77 ± 2.529		MMRM/12w[a]
Ist 20 mg	194	9.68 ± 2.298	179	10.55 ± 3.230	179	1.01 ± 2.697		
Ist 40 mg	200	9.72 ± 2.349	176	10.32 ± 3.163	176	0.77 ± 2.536		
Rx Diff 20mg						0.24	0.366 (-0.28, 0.77)	
Rx Diff 40mg						0.00	0.986 (-0.52, 0.53)	

Reviewer Comment(s)

Table 42 shows results of istradefylline in Study 014 on ON time without troublesome dyskinesia. The DNP has considered this diary based efficacy outcome as critically important for showing a therapeutic benefit when a primary efficacy endpoint showing a decrease in a variable of outcome of OFF time was statistically significant and arguing for a drug benefit. The mean treatment difference (vs placebo) was not statistically significant for either dose. Of great interest, the change from baseline for the high dose 40 mg showed a mean treatment different of 0 with a p value of nearly 1 despite the fact that large numbers of patients (approaching 200 per treatment group) had been studied in this trial. This observation supports the view that there was NO benefit of istradefylline in this trial. This observation is unique in my experience of seeing NDA data for Parkinson's disease for over 20 years. More specifically, it is highly unusual for a drug ultimately considered to be effective and subsequently approved by FDA to be associated with results from a large pivotal trial in which there was NOT even any numerical benefit (i.e., 0 treatment difference vs placebo) for a key, important efficacy endpoint. Considering that all patients in this trial were not Japanese, I consider this observation to be very problematic for suggesting efficacy of istradefylline in a non-Japanese population. It is also important to recognize that this study (014) was specifically planned in close collaboration with the Agency/DNP to address Agency concerns that a study should be planned in which istradefylline was adjunctive to additional "optimal" treatment of Parkinson's disease.

Because all efficacy results in trial (Study 014) were not statistically significant, I will present selected tables of more important efficacy endpoints and then provide comments on

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all these tables at the end of these tables instead of making a comment immediately after each table.

Table 43 Total Hours per Day ON With Troublesome Dyskinesia at Week 12/16 Actual and Change from Baseline - Observed Case Analysis – mITT

Study	Baseline		Post-Baseline		CFB		P Value (Two-sided) (95% CI)	Comment
	n	Mean ± SD	n	LSM ± SD	n	LSM ± SD		
6002-014 (mITT)								
Placebo	198	1.11 ± 1.957	188	0.81 ± 2.161	188	-0.08 ± 1.204		MMRM/12w[a]
Ist 20 mg	194	0.80 ± 1.596	179	0.94 ± 2.142	179	0.04 ± 1.300		
Ist 40 mg	200	0.84 ± 1.353	176	1.01 ± 1.836	176	0.12 ± 1.412		
Rx Diff 20mg						0.13	0.346 (-0.14, 0.40)	
Rx Diff 40mg						0.20	0.145 (-0.07, 0.47)	

Table 44 Total Hours per Day Asleep at Week 12/16 Actual and Change from Baseline - Observed Case Analysis – mITT

Study	Baseline		Post-Baseline		CFB		P Value (Two-sided) (95% CI)	Comment
	n	Mean ± SD	n	LSM ± SD	n	LSM ± SD		
6002-014 (mITT)								
Placebo	198	8.11 ± 1.741	188	8.26 ± 1.606	188	0.17 ± 1.189		MMRM/12w[a]
Ist 20 mg	194	8.04 ± 1.575	179	8.19 ± 1.803	179	0.10 ± 1.274		
Ist 40 mg	200	8.11 ± 1.591	176	8.33 ± 1.897	176	0.23 ± 1.345		
Rx Diff 20mg						-0.07	0.564 (-0.33, 0.18)	
Rx Diff 40mg						0.06	0.620 (-0.19, 0.32)	

Table 45 Percentage of Awake OFF Time per Day at Week 12/16 Actual and Change from Baseline - Observed Case Analysis – mITT

Study	Baseline		Post-Baseline		CFB		P Value (Two-sided) (95% CI)	Comment
	n	Mean ± SD	n	LSM ± SD	n	LSM ± SD		
6002-014 (mITT)								
Placebo	198	34.55 ± 12.158	188	28.43 ± 17.503	188	-5.52 ± 14.575		MMRM/12w[a]
Ist 20 mg	194	33.92 ± 11.792	179	26.70 ± 15.278	179	-7.25 ± 15.389		
Ist 40 mg	200	33.16 ± 12.710	176	27.03 ± 15.590	176	-6.92 ± 13.065		
Rx Diff 20mg						-1.73	0.230 (-4.56, 1.10)	
Rx Diff 40mg						-1.40	0.330 (-4.23, 1.42)	

Table 46 Percentage of Awake ON Time Without Troublesome Dyskinesia per Day at Week 12/16 Actual and Change from Baseline - Observed Case Analysis – mITT

Study	Baseline		Post-Baseline		CFB		P Value (Two-sided) (95% CI)	Comment
	n	Mean ± SD	n	LSM ± SD	n	LSM ± SD		
6002-014 (mITT)								
Placebo	198	58.54 ± 15.121	188	66.29 ± 21.338	188	5.89 ± 15.792		MMRM/12w[a]
Ist 20 mg	194	61.04 ± 13.299	179	67.48 ± 19.331	179	7.08 ± 16.685		
Ist 40 mg	200	61.54 ± 13.520	176	66.37 ± 18.857	176	5.97 ± 15.591		
Rx Diff 20mg						1.19	0.476 (-2.09, 4.47)	
Rx Diff 40mg						0.07	0.964 (-3.20, 3.34)	

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Table 47 Percentage of Awake ON Time with Troublesome Dyskinesia per Day at Week 12/16
Table 47Actual and Change from Baseline - Observed Case Analysis – mITT

Study	Baseline		Post-Baseline		CFB		P Value (Two-sided) (95% CI)	Comment
	n	Mean ± SD	n	LSM ± SD	n	LSM ± SD		
6002-014 (mITT)								
Placebo	198	6.90 ± 11.775	188	5.20 ± 13.425	188	-0.45 ± 7.579		MMRM/12w[a]
Ist 20 mg	194	5.05 ± 9.904	179	5.81 ± 12.733	179	0.16 ± 7.543		
Ist 40 mg	200	5.30 ± 8.585	176	6.56 ± 12.193	176	0.91 ± 9.433		
Rx Diff 20mg						0.61	0.477 (-1.08, 2.31)	
Rx Diff 40mg						1.36	0.114 (-0.33, 3.05)	

Table 48 UPDRS Part II (Activities of Daily Living-ADL) During ON at Week 12 - Actual and Change from Baseline - Observed Case Analysis - mITT Analysis Set

Study	Baseline		Post-Baseline		CFB		P Value (Two-sided) (95% CI)	Comment
	n	Mean ± SD	n	LSM ± SD	n	LSM ± SD		
6002-014 (mITT)								
Placebo	198	12.2 ± 5.30	188	11.2 ± 5.37	188	-1.2 ± 3.63		MMRM/12w[a]
Ist 20 mg	194	12.0 ± 5.71	181	11.2 ± 5.95	181	-1.3 ± 4.23		
Ist 40 mg	200	13.1 ± 5.85	178	11.2 ± 5.80	178	-1.3 ± 3.55		
Rx Diff 20mg						-0.1	0.858 (-0.8, 0.7)	
Rx Diff 40mg						-0.1	0.875 (-0.8, 0.7)	

Table 49 UPDRS Part III (Motor) During ON at Week 12 - Actual and Change from Baseline - Observed Case Analysis - mITT Analysis Set

Study	Baseline		Post-Baseline		CFB		P Value (Two-sided) (95% CI)	Comment
	n	Mean ± SD	n	LSM ± SD	n	LSM ± SD		
6002-014 (mITT)								
Placebo	198	22.0 ± 10.81	188	19.9 ± 10.34	188	-2.8 ± 6.80		MMRM/12w[a]
Ist 20 mg	194	22.6 ± 11.48	181	19.8 ± 12.29	181	-2.9 ± 7.33		
Ist 40 mg	200	23.5 ± 12.13	178	18.9 ± 11.22	178	-3.8 ± 7.53		
Rx Diff 20mg						-0.1	0.884 (-1.4, 1.2)	
Rx Diff 40mg						-1.0	0.141 (-2.3, 0.3)	

Table 50 Clinical Global Impression-Improvement (CGI-I) Frequencies at Week 12 – mITT Analysis Set

Parameter Score	Placebo N=198 (%)	Istradefylline 20 mg/d N=194 (%)	Istradefylline 20 mg/d Difference (95% CI)	Istradefylline 40 mg/d N=200 (%)	Istradefylline 40 mg/d Difference (95% CI)
Overall Condition					
n (%)	188	181		177	
1: ≥ moderate improvement	32 (17.0)	38 (21.0)	4.0% (-4.0, 12.0)	29 (16.4)	-0.6% (-8.3, 7.0)
2: mild improvement	59 (31.4)	62 (34.3)	2.9% (-6.7, 12.5)	60 (33.9)	2.5% (-7.1, 12.1)
3: no change from baseline	72 (38.3)	52 (28.7)	-9.6% (-19.1, 0.0)	59 (33.3)	-5.0% (-14.8, 4.9)
4: mild deterioration	20 (10.6)	26 (14.4)	3.7% (-3.0, 10.5)	23 (13.0)	2.4% (-4.3, 9.0)
5: ≥ moderate deterioration	5 (2.7)	3 (1.7)	-1.0% (-4.0, 2.0)	6 (3.4)	0.7% (-2.8, 4.3)
P value			0.197		0.872

Reviewer Comment(s)

- Table 43 shows that there were small increases (0,13-0.20 hours) in the change from

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baseline for ON with troublesome dyskinesia but that these increases were not statistically significant.

- Table 44 shows that there was no appreciable change from baseline change in sleep time.

- Table 45 shows that there were small decreases for change from baseline in percentage of awake OFF time. These decreases were not statistically significant and were not dose-dependent.

- Table 46 shows that there was a small increase for the change from baseline for percentage of awake ON time without troublesome dyskinesia for the 20 mg dose and no appreciable change for the 40 mg dose. These small changes were not statistically significant.

- Table 47 shows that there were small increases in the change from baseline for the percentage of awake ON time with troublesome dyskinesia. The increase for the 40 mg dose was greater than that for the 20 mg dose but neither increase was statistically significant.

- Table 48 shows a similar, minimal decreases in change from baseline for UPDRS Part II-ADL which were not statistically significant.

- Table 49 shows a minimal decease for change from baseline for UPDRS Part III (motor subscale) for the 20 mg dose and a larger decrease for the 40 mg dose. Neither change was statistically significant.
- Table 50 shows scoring for Clinical Global Impression-Improvement. Neither dose showed statistically significant improvement.

Dose/Dose Response

Reviewer Comment(s)

In Study 0608, there appeared to be a dose-response for the important diary based efficacy endpoints (i.e., total ON without troublesome dyskinesia, total OFF, percentage ON without troublesome dyskinesia while awake, percentage OFF while awake) with the 40 mg dose showing greater effects than those of the 20 mg dose. However, in Study 009, there did not appear to be a dose-response for these same efficacy endpoints because positive results were similar for both doses and in some instances results for the 20 mg dose were numerically slightly greater than the corresponding results for the 40 mg dose. The original review by the Agency did not conclude that there was evidence for dose response. It is also relevant to note that the sponsor's analyses of exposure response did not suggest greater efficacy with greater exposure of circulating istradefylline levels. The FDA's Clinical Pharmacology team concurs with this conclusion.

Durability of Response and Persistence of Effect

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Reviewer Comment(s)

In general, when a statistically significant effect was observed for an efficacy endpoint in Studies 0608 and 009, a noteworthy numerical benefit was usually observed after 2 weeks of treatment and this effect was occasionally statistically significant based upon a nominal p value. The effect generally appeared to be durable and persist throughout the trial.

Additional Analyses Conducted on the Individual Trial

There were no additional analyses which are relevant to presentation here for these individual trials.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Table 51 shows the number of patients in each of the 8 pivotal trials according randomized treatment.

Table 51 Numbers ITT/FAS Patients in All 8 Randomized, Placebo-Controlled Pivotal Trials By Treatment

Trial	N for Placebo	N for Istradefylline 10 mg Daily	N for Istradefylline 20 mg Daily	N for Istradefylline 40 mg Daily	N for Istradefylline 60 mg Daily
005	66			129	
006	77		163		155
013	113		112		
018	146	149	144	145	
007	151			158	
0608	118		115	124	
009	123		120	123	
014	198		194	200	
Total	892	149	848	879	155

Source of Data: TITT=Intent-to-Treat; FAS=Full Analysis Set
Table created by Clinical Reviewer based upon sponsor Table 2.1-2 in ISE

Prior to considering efficacy across pivotal trials, it is important to consider the comparability of patients enrolled in these trials. A review of baseline characteristics (demographic and information related to Parkinson's disease and its treatment) can provide insight into this comparability. **Error! Reference source not found.** Table 52 compares these baseline characteristics of patients in all 8 pivotal trials. APPEARS THIS WAY ON ORIGINAL

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Table 52 Patient Demographic Characteristics by Study (ITT Analysis Set) All 8 Pivotal Trials

Characteristic	6002-US-005 N=195 n (%)	6002-US-006 N=395 n (%)	6002-US-013 N=225 n (%)	6002-0608 N=357 n (%)	6002-009 N=366 n (%)	6002-US-018 N=584 n (%)	6002-EU-007 N=455 n (%)	6002-014 N=592 n (%)
Age (years)								
n	195	395	225	357	366	584	455	592
Mean	63.2	64.0	63.4	64.6	65.8	63.1	61.5	64.0
SD	9.34	10.31	9.80	7.83	8.70	8.92	9.41	8.37
Median	64.0	65.0	63.0	65.0	67.0	63.0	62.0	64.0
Range[a]	38.0-87.0	36.0-87.0	36.0-87.0	37.0-84.0	33.0-84.0	35.0-85.0	34.0-87.0	41.0-87.0
Gender, n (%)								
Male	117 (60.0)	264 (66.8)	150 (66.7)	150 (42.0)	162 (44.3)	389 (66.6)	278 (61.1)	363 (61.3)
Female	78 (40.0)	131 (33.2)	75 (33.3)	207 (58.0)	204 (55.7)	195 (33.4)	177 (38.9)	229 (38.7)
Race, n (%)								
White	186 (95.4)	367 (92.9)	211 (93.8)	0	0	545 (93.3)	310 (68.1)	572 (96.6)
Black or African American	3 (1.5)	7 (1.8)	5 (2.2)	0	0	7 (1.2)	0	4 (0.7)
Asian	2 (1.0)	12 (3.0)	6 (2.7)	357 (100.0)	366 (100.0)	13 (2.2)	95 (20.9)	8 (1.4)
Hispanic	2 (1.0)	6 (1.5)	2 (0.9)	0	0	17 (2.9)	43 (9.5)	0
American Indian or Alaska Native	1 (0.5)	1 (0.3)	0	0	0	1 (0.2)	0	1 (0.2)
Native Hawaiian or Other Pacific Islander	1 (0.5)	0)	1 (0.4)	0	0	0	0	0
Other	0	2 (0.5)	0	0	0	1 (0.2)	7 (1.5)	7 (1.2)
Weight (kg)								
n	195	395	225	357	366	582	455	592
Mean	79.36	77.68	81.01	54.22	55.57	81.83	70.25	79.32
SD	19.209	16.890	18.448	10.841	12.07	17.662	14.246	16.199
Median	76.70	77.60	78.90	54.00	54.45	81.60	69.0	78.90
Range[a]	40.9-191.4	42.4-133.0	43.3-137.1	32.0-94.5	32.0-113.0	39.8-150.1	31.4-122.8	45.4-143.8
BMI (kg/m^2)								
n	195	394	225	357	366	582	455	592
Mean	26.67	26.26	27.02	21.87	22.29	28.05	25.32	27.15
SD	5.150	4.541	5.179	3.449	3.541	5.367	4.280	4.888
Median	25.90	26.00	26.40	21.60	22.20	27.45	24.90	26.60
Range[a]	17.8-57.2	15.9-45.4	17.2-44.9	13.8-32.5	14.2-40.0	15.7-54.4	14.4-45.2	16.3-46.5
Current Smoker, n (%)								
Yes	13 (6.7)	18 (4.6)	11 (4.9)	28 (7.8)	20 (5.5)	27 (4.6)	23 (5.1)	26 (4.4)
No	182 (93.3)	377 (95.4)	214 (95.1)	329 (92.2)	346 (94.5)	557 (95.4)	432 (94.9)	566 (95.6)

a: Range=minimum to maximum value.
BMI=body mass index; ITT=intent-to-treat; RCT=randomized controlled trial; SD=standard deviation
Source: Tables 5.3.5.3.1-1.3.1; 5.3.5.3.1-1.3.2; 5.3.5.3.1-1.3.3; 5.3.5.3.1-1.3.4; 5.3.5.3.1-1.3.5; 5.3.5.3.1-1.3.6; 5.3.5.3.1-1.3.7; 5.3.5.3.1-1.3.8

Reviewer Comment(s)

Overall, the demographic characteristics for all 8 pivotal trials were relatively similar with the exception of weight. The mean/median weight was approximately 75 kg for both Japanese pivotal trials (0608, 009). However, in marked contrast, five of six pivotal trials outside of Japan which included a significant percentage of patients in the U.S. showed a mean/median weight ranging approximately between 75-80 kg. The other pivotal trial outside of Japan (007) showed a mean/median weight of approximately 70 kg which was also much greater than mean/median weight in the Japanese trials.

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Table 53 Parkinson's Disease History and Baseline Characteristics (ITT Analysis Set) All 8 Pivotal Trials

	6002-US-005 N=195 n (%)	6002-US-006 N=395 n (%)	6002-US-013 N=225 n (%)	6002-0608 N=357 n (%)	6002-009 N=366 n (%)	6002-US-018 N=584 n (%)	6002-EU-007 N=455 n (%)	6002-014 N=592 n (%)
Time Since Diagnosis (years)[a]								
n	195	395	225	357	366	584	454	--
Mean	9.9	9.5	9.4	8.2	7.7	8.9	8.3	--
SD	4.99	5.03	5.05	4.32	4.40	4.78	4.42	--
Median	9.0	8.8	8.0	7.6	6.8	7.8	7.9	--
Range (min-max)	1.4-28.4	1.7-32.3	0.1-36.8	0.4-30.7	0.6-26.0	1.0-30.4	0.2-29.4	--
< 6 years	42 (21.5)	98 (24.8)	56 (24.9)	128 (35.9)	156 (42.6)	176 (30.1)	154 (33.8)	--
≥ 6 to < 13 years	101 (51.8)	218 (55.2)	121 (53.8)	180 (50.4)	165 (45.1)	306 (52.4)	246 (54.1)	--
≥ 13 years	52 (26.7)	79 (20.0)	48 (21.3)	49 (13.7)	45 (12.3)	102 (17.5)	54 (11.9)	--
Missing	0	0	0	0	0	0	1 (0.2)	--
1-3 years	--	--	--	--	--	--	--	24 (4.1)
4-7 years	--	--	--	--	--	--	--	203 (34.3)
8 years or greater	--	--	--	--	--	--	--	365 (61.7)
Time Since Initiation of Levodopa (years)								
n	--	--	225	--	--	584	452	591
Mean	--	--	8.1	--	--	7.5	7.2	8.7
SD	--	--	5.05	--	--	4.76	4.21	4.38
Median	--	--	7.5	--	--	6.6	6.7	8.0
Range (min-max)	--	--	1.1-31.8	--	--	0.4-30.4	0.9-28.4	2.0-28.0
Not collected	195 (100.0)	395 (100.0)	0	357 (100.0)	366 (100.0)	0	0	0
Missing	--	--	0	--	--	0	3 (0.7)	1 (0.2)
< 5 years	--	--	68 (30.2)	--	--	206 (35.3)	159 (34.9)	88 (14.9)
≥ 5 to < 11 years	--	--	107 (47.6)	--	--	263 (45.0)	225 (49.5)	331 (55.9)
≥ 11 to < 21 years	--	--	46 (20.4)	--	--	106 (18.2)	63 (13.8)	158 (26.7)
≥ 21 years	--	--	4 (1.8)	--	--	9 (1.5)	5 (1.1)	14 (2.4)
Time Since Onset of Motor Complications (years)								
n	195	395	225	357	366	582	453	587
Mean	4.1	4.5	3.8	3.3	3.3	3.6	3.1	6.0
SD	3.51	3.86	3.53	2.81	3.09	3.44	2.81	4.25
Median	3.0	3.2	2.8	2.7	2.5	2.5	2.3	5.0
Range (min-max)	0.0-18.3	0.1-29.9	01-24.8	0.1-19.2	0.0-22.0	0.0-24.4	0.1-18.9	1.0-25.0
< 4 years	121 (62.1)	221 (55.9)	143 (63.6)	243 (68.1)	263 (71.9)	395 (67.6)	323 (71.0)	211 (35.6)
≥ 4 to < 7 years	38 (19.5)	92 (23.3)	49 (21.8)	80 (22.4)	60 (16.4)	104 (17.8)	97 (21.3)	163 (27.5)
≥ 7	36 (18.5)	82 (20.8)	33 (14.7)	34 (9.5)	43 (11.7)	83 (14.2)	33 (7.3)	213 (36.0)
Missing	0	0	0	0	0	2 (0.3)	2 (0.4)	5 (0.8)
Total Hours per Day Spent in the OFF State (hours) - Observed Case								
n	195	395	225	357	366	584	455	592
Mean	6.31	5.87	6.62	6.58	6.28	6.70	6.41	5.36
SD	2.632	2.461	2.479	2.680	2.552	2.140	2.189	2.007
Median	6.00	5.80	6.30	6.30	5.95	6.50	6.00	5.17
Range (min-max)	0.0 to 14.5	0.8 to 14.8	2.5 to 17.8	2.0 to 17.0	1.9 to 14.2	2.0 to 16.3	2.0 to 14.0	1.0 to 14.3
Total Daily Dosage of Levodopa at Study Entry (mg)								
n	195	390	224	357	366	584	454	592
Mean	785.1	744.5	775.4	416.2	429.1	771.4	637.5	829.3
SD	505.42	371.64	389.00	140.13	146.24	383.56	323.54	374.88
Median	700.0	700.0	700.0	400.0	400.0	750.0	600.0	750.0
Range (min-max)	150 to 4800	75 to 2200	150 to 2100	300 to 1500	300 to 1200	25 to 3000	105 to 2000	300 to 3150
Modified Hoehn and Yahr Scale (OFF State)[a]								
Stage 2	0	0	75 (33.3)	19 (5.3)	26 (7.1)	182 (31.2)	73 (16.0)	270 (45.6)
Stage 2.5	0	0	63 (28.0)	44 (12.3)	45 (12.3)	156 (26.7)	141 (31.0)	155 (26.2)
Stage 3	0	0	70 (31.1)	170 (47.6)	145 (39.6)	190 (32.5)	191 (42.0)	147 (24.8)
Stage 4	0	0	17 (7.6)	124 (34.7)	150 (41.0)	56 (9.6)	50 (11.0)	20 (3.4)
Missing[b]	195 (100.0)	395 (100.0)	0	0	0	0	0	0
UPDRS Part III Score[c] in the ON State								
n	182	388	219	357	366	558	444	592
Mean	17.8	17.0	23.4	20.9	21.2	22.1	27.5	22.7
SD	11.08	9.42	11.23	10.31	11.13	11.37	11.84	11.49
Median	16.0	16.0	23.0	20.0	21.0	21.0	27.0	21.0
Range (min-max)	1 to 51	0 to 57	0 to 54	0 to 61	1 to 58	0 to 65	1 to 68	2 to 68

a: Baseline modified Hoehn and Yahr scale was measured in the ON state in Study 6002-014 and in the OFF state for the other 7 studies.
b: Modified Hoehn and Yahr scale was not recorded on the case report form at baseline for Studies 6002-US-005 and 6002-US-006.
c: UPDRS Part III score=Sum of UPDRS questions 18 to 31 (motor examination).
ITT=intent-to-treat; max= maximum; min=minimum; RCT=randomized controlled trial; SD=standard deviation; UPDRS=Unified Parkinson's Disease Rating Scale
Source: Tables 5.3.5.3.1-1.3.1; 5.3.5.3.1-1.3.2; 5.3.5.3.1-1.3.3; 5.3.5.3.1-1.3.4; 5.3.5.3.1-1.3.5; 5.3.5.3.1-1.3.6; 5.3.5.3.1-1.3.7; 5.3.5.3.1-1.3.8, 5.3.5.3.1-1.4.2.1; 5.3.5.3.1-1.4.2.2; 5.3.5.3.1-1.4.2.3; 5.3.5.3.1-1.4.2.4; 5.3.5.3.1-1.4.2.5; 5.3.5.3.1-1.4.2.6; 5.3.5.3.1-1.4.2.7; 5.3.5.3.1-1.4.2.8

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Reviewer Comment(s)

Overall, the baseline characteristics for Parkinson's disease were relatively similar across all pivotal trials. This observation supported the view that similar patients with regard to these characteristics had been studied in these trials.

7.1.1. Primary Endpoints and Secondary Endpoints

I created summary Table 54 and Table 55 primarily based upon DNP requested analyses included in the Integrated Summary of Efficacy (ISE) shown in Tables 5.3.5.3.1-2.7.1 through 5.3.5.3.1-2.7.11 and in some instances from results in respective final study reports. These key tables show what I consider to be results of important efficacy endpoints (including primary efficacy endpoints and also selected secondary efficacy endpoints) across each pivotal trial according to an MMRM statistical analyses (the main statistical analysis used in the ISE) and also according to the primary, pre-specified statistical analysis (ANOVA, ANCOVA with Last Observation Carried Forward-LOCF imputation, or MMRM) for each pivotal trial. The modified Intent-to-Treat (mITT) population consisting of patients who received treatment and had baseline data for the endpoint, and at least one post-baseline/treatment was analyzed. Of particular note, Table 55 shows results for the primary prespecified statistical analysis (ANOVA) for studies 005 and 006 and also results for ANCOVA which had been specified as a supplementary/supportive analysis. Results for each of the 5 pivotal trials originally submitted with this NDA are shown on the left side of each table and results of the 3 new pivotal trials (which are shaded in grey) are shown on the right side of each table. Orange shading in each table depicts the primary efficacy endpoint (percentage awake time in OFF state in original 5 trials or total OFF hours in 3 new trials) for each pivotal trial. As outlined previously, because a decrease in OFF is not necessarily a beneficial therapeutic effect, green shading depicts a key efficacy endpoint which would show a direct therapeutic benefit of treatment (i.e., an increase of percentage or total daily hours of ON time without troublesome dyskinesia) relative to the primary efficacy endpoint (i.e., a change such as a decrease of percentage or total daily OFF hours). In addition, yellow highlighting indicates that the effect is not statistically significant and red font indicates numerical worsening (opposite effect than desired) of the result for the efficacy endpoint or a very minimal (less than 0.1 hour/6 minutes or, numerical effect in a “positive” direction on the endpoint.

Analyses of results for ON without troublesome dyskinesia (as change in percent of daily awake time or in total hours) were not pre-specified in the SAPs for studies 005 and 006 but were conducted as post-hoc analyses after data were unblinded. However, analyses for these secondary efficacy endpoints were prospectively planned and pre-specified in the SAPs of studies 007, 009, 013, 014, 018, and 0608.

My review will present my comments for each individual, pivotal trial for the primary efficacy endpoints and important secondary efficacy endpoints which are presented in Table 54 and Table 55. In addition, I will outline my perspective on how I view and consider the overall efficacy results from each trial. I will focus initially on results in Table 55 according to the primary, pre-specified statistical analysis and will comment on the robustness of results relative to statistical

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analyses which had not been pre-specified (e.g., ANCOVA or MMRM). P values described are nominal p values which have not been corrected/adjusted for multiplicity/multiple comparisons.

The sponsor provided the following description for the models for the MMRM and ANCOVA statistical analyses:

- MMRM: Difference in LS means, 95% CI and p-value are from paired comparisons between each istradefylline treatment arm vs placebo. A mixed model repeated measures approach was used with baseline assessment as a covariate, and study center, treatment group, week treatment-by-week interaction as fixed effect terms

- ANCOVA: Difference in LS means, 95% CI and p-value are from paired comparisons between each istradefylline treatment arm vs placebo. An ANCOVA model was used with baseline assessment as a covariate, and study center and treatment group as fixed effect terms

Efficacy results for UPDRS Part II (Activities of Daily Living-ADL) and for UPDRS Part III (Motor subscale) are shown for all trials. Although efficacy endpoints are typically key efficacy endpoints for patients with early Parkinson's disease (particularly patient receiving treatment as monotherapy and not taking any dopaminergic drugs), not infrequently results from trials of patients with advanced Parkinson's disease show substantial numerical effects in favor of a benefit and sometimes statistically significant effects ($p < 0.05$) for nominal p values.

Regardless of whether my comments explicitly specify my interpretation of results, my comments will focus on the mean treatment difference (vs placebo) of any efficacy endpoint discussed/outlined unless my comments are otherwise specified.

Overall the concordance for statistically significant results between the primary statistical analysis (ANOVA or ANCOVA) and MMRM analysis was extremely high (i.e., concordance for more than 90 % of potential comparisons of individual cells). My review will comment on instances in which the result with the primary analysis ANOVA or ANCOVA did not seem robust because the ANOVA or ANCOVA result was statistically significant ($P < 0,05$) and the MMRM analysis result was not statistically significant ($P > 0,05$).

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Table 54 **LSM Treatment Difference (Istradefylline – Placebo) for Important Efficacy Endpoints for mITT Population (N=All Drug+Placebo) in Individual Pivotal Studies According to MMRM Statistical Analysis (Yellow Highlight Indicates Not Statistically Significant; P>0.05)**

Efficacy Endpoint Change from Baseline	Study 005 NA mITT= 195	Study 006 NA mITT=395		Study 013 US mITT= 225	Study 018 NA mITT=584			Study 007, EU/SA/ AS/SAF mITT= 309	Study 608 Japan mITT=357		Study 009 Japan mITT=369		Study 014* NA/EU/Is mITT=592	
	40 mg	20 mg	60 mg	20 mg	10 mg	20 mg	40 mg	40 mg	20 mg	40 mg	20 mg	40 mg	20 mg	40 mg
ON WO TD Hours/Day	+1.03 P=0.015	+0.70 P=0.076	+0.55 P=0.171	+0.44 P=0.258	-0.40 P=0.237	-0.15 P=0.636	-0.01 P=0.976	-0.01 P=0.762	+0.59 P=0.079	+0.57 P=0.082	+0.98 P=0.002	+0.80 P=0.012	+0.24 P=0.366	0 P=0.986
% Awake Time ON WO TD/Day	+5.81 P=0.025	+3.18 P=0.159	+3.60 P=0.120	+3.16 P=0.159	-2.31 P=0.241	-1.46 P=0.663	-0.01 P=0.995	-1.17 P=0.546	+3.32 P=0.096	+3.40 P=0.082	+5.37 P=0.007	+4.48 P=0.022	+1.19 P=0.476	+0.07 P=0.964
OFF Hours/Day	-1.11 P=0.004	-0.61 P=0.077	-0.76 P=0.033	-0.62 P=0.081	+0.32 P=0.294	+0.25 P=0.425	0 P=0.998	-0.01 P=0.983	-0.65 P=0.031	-0.82 P=0.006	-0.77 P0.007	-0.73 P=0.010	-0.32 P=0.156	-0.27 P=0.234
% Awake Time OFF/Day	-6.38 P=0.006	-4.21 P=0.038	-4.32 P=0.038	-4.00 P=0.059	+1.83 P=0.319	+1.32 P=0.477	-0.41 -0.824	-0.16 P=0.927	-3.91 P=0.035	-4.98 P=0.006	-5.15 P=0.004	-4.60 P=0.10	-1.73 P=0.230	-1.40 P=0.330
UPDRS Part II (ON) (ADL)	-0.6 P=0.195	-0.1 P=0.813	-0.4 P=0.352	-0.7 P=0.123	+0.1 P=0.725	-0.1 P=0.819	-0.3 P=0.408	-0.5 P=0.185	0 P=0.954	-0.2 P=0.500	+0.1 P=0.763	-0.1 P=0.649	-0.1 P=0.858	-0.1 P=0.875
UPDRS Part III (ON) (Motor)	-0.5 P=0.676	-0.5 P=0.546	-0.9 P=0.327	-1.1 P=0.328	-0.6 P=0.489	-0.7 P=0.451	-2.3 P=0.014	-1.2 P=0.192	-2.2 P=0.008	-2.0 P=0.014	-0.9 P=0.193	-2.0 P=0.005	-0.1 P=0.884	-1.0 P=0.141
CGI-I	P=0.326	P=0.666	P=0.136	P=0.640	P=0.640	P=0.953	P=0.564	P=0.729	P=0.074	P=0.096	P=0.005	P<0.001	P=0.197	=0.872

Shading: Grey = 3 new pivotal trials; Orange = Primary Efficacy Endpoint; Green = Complimentary efficacy endpoint to primary endpoint reflecting direct benefit
NA=North America; US=United States; EU=European Union; SA=South America; AS=Asia; SAF=South Africa; Is-Israel
* Key pivotal study planned (starting in 2012) closely with DNP to address DNP efficacy concerns despite known efficacy results of Japanese studies (0608; 009) at the time
mITT=modified Intent-To-Treat (total N for placebo and all istradefylline groups)
CGI-I (Clinical Global Impression-Improvement) statistically tested with Cochran-Mantel-Haenszel or Wlicoxon tests
Red font indicates numerical worsening effect on efficacy endpoint or minimal, numerical, positive effect (i.e., less than 0.1 hour/6 minutes or less than 1 %)
Table created by reviewer based upon various sponsor data analyses

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Table 55 **LSM Treatment Difference (Istradefylline – Placebo) for Important Efficacy Endpoints for mITT Population (N=All Drug+Placebo) in Individual Pivotal Studies According to Pre-Specified Statistical Analysis (Yellow Highlight Indicates Not Statistically Significant; P>0.05 and Primary Statistical Model)**

Efficacy Endpoint Change from Baseline Treatment Difference	Stat Mod-el	Study 005 NA mITT=195 ANOVA Primary Analysis ANCOVA (Supple-mentary Analysis)	Study 006 NA mITT=395 ANOVA Primary Analysis ANCOVA (Supportive Analysis)		Study 013 US mITT=225 ANCOVA Primary Analysis	Study 018 NA mITT=584 ANCOVA Primary Analysis			Study 007 EU/SA/AS/SAF mITT=309 ANCOVA Primary Analysis	Study 608 Japan mITT=357 ANCOVA Primary Analysis		Study 009 Japan mITT=369 ANCOVA Primary Analysis		Study 014 NA/EU/Is mITT=592 MMRM Primary Analysis	
		40 mg	20 mg	60 mg	20 mg	10 mg	20 mg	40 mg	40 mg	20 mg	40 mg	20 mg	40 mg	20 mg	40 mg
ON WO TD Hours/Day	ANO	+0.97 P=0.037	+0.93 P=0.021	+0.63 P=0.124										+0.24 P=0.366	0 P=0.986
	ANC	+1.01 P=0.013	+0.71 P=0.062	+0.60 P=0.118	+0.55 P=0.135	-0.45 P=0.168	-0.18 P=0.584	-0.03 P=0.934	-0.03 P=0.929	+0.57 P=0.086	+0.64 P=0.048	+0.91 P=0.004	+0.86 P=0.005		
% Awake Time ON WO TD/Day	ANO	+5.60 P=0.037	+3.89 P=0.096	+3.55 P=0.134										+1.19 P=0.476	+0.07 P=0.964
	ANC	+5.83 P=0.021	*+3.52* P=0.109	+4.04 P=0.070	+3.87 P=0.072	-2.40 P=0.212	-1.55 P=0.422	-0.12 P=0.952	-0.88 P=0.646	+3.12 P=0.115	+3.78 P=0.052	+4.96 P=0.010	+4.76 P=0.12		
OFF Hours/Day	ANO	-1.15 P=0.006	-0.39 P=0.286	-0.55 P=0.140										-0.32 P=0.156	-0.27 P=0.234
	ANC	-1.08 P=0.005	-0.64 P=0.055	-0.77 P=0.023	-0.73 P=0.033	+0.30 P=0.310	+0.28 P=0.360	-0.03 P=0.970	-0.07 P=0.820	-0.63 P=0.034	-0.90 P=0.002	-0.74 P=0.007	-0.77 P=0.005		
% Awake Time OFF/Day	ANO	-6.78 P=0.007	-3.65 P=0.088	-3.77 P=0.082										-1.73 P=0.230	-1.40 P=0.330
	ANC	-6.38 P=0.006	-4.36 P=0.026	-4.49 P=0.024	-4.57 P=0.025	+1.79 P+0.319	+1.50 P=0.408	-0.66 P=0.714	-0.61 P=0.729	-3.78 P=0.039	-5.46 P=0.002	-4.93 P=0.005	-4.92 P=0.004		
UPDRS Part II (ADL) ON	ANO	-0.6 P=0.228	-0.2 P=0.542	-0.2 P=0.715										-0.1 P=0.858	-0.1 P=0.875
	ANC	-0.6 P=0.195	0 P=0.949	-0.2 P=0.616	+0.50 P=0.211	+0.2 P=0.600	0 P=0.975	-0.1 P=0.820	-0.6 P=0.116	0 P=0.922	-0.2 0.542	0 P=0.866	-0.1 P=0.536		
UPDRS Part III (Motor) ON	ANO	-0.2 P=0.822	-0.69 P=0.462	-1.02 P=0.280										-0.1 P=0.884	-1.0 P=0.141
	ANC	-0.3 P=0.791	-0.30 P=0.732	-087 P=0.320	-0.9 P=0.411	-0.5 P=0.572	0 P=0.959	-2.1 P=0.028	-1.6 P=0.064	-2.0 P=0.013	-2.0 P=0.012	-0.9 P=0.178	-2.1 P=0.002		
CGI-I		P=0.326	P=0.666	P=0.136	P=0.640	P=0.640	P=0.953	P=0.564	P=0.729	P=0.074	P=0.096	P=0.005	P-<0.001	P=0.197	=0.872

Shading: Grey = 3 new pivotal trials; Orange = Primary Efficacy Endpoint; Green = Complimentary efficacy endpoint to primary endpoint reflecting direct benefit
NA=North America; US=United States; EU=European Union; SA=South America; AS=Asia; SAF=South Africa; Is-Israel
*** Key pivotal study planned (starting in 2012) closely with DNP to address DNP efficacy concerns despite known efficacy results of Japanese studies (0608; 009) at the time**
Statistical Model: ANO = ANOVA with LOCF; ANC = ANCOVA with LOCF; mITT=modified Intent-To-Treat (total N for placebo and all istradefylline groups)
CGI-I (Clinical Global Impression-Improvement) statistically tested with Cochran-Mantel-Haenszel or Wlicoxon tests
Red font indicates numerical worsening effect on efficacy endpoint or minimal, numerical, positive effect (i.e., less than 0.1 hours/6 minutes or less than 1%)
Table created by reviewer based upon various sponsor data analyses

Study 005 (North America)

Reviewer Comment(s)

- Istradefylline (40 mg) showed a statistically significant decrease on the mean treatment difference (vs placebo) for the primary efficacy endpoint, change from baseline in change from baseline for percentage of daily awake OFF time for the primary, pre-specified statistical analysis (ANOVA). Istradefylline also showed a statistically significant increase on change of percentage of ON time without troublesome dyskinesia, a corresponding, important efficacy endpoint to the primary efficacy endpoint because it indicates a direct therapeutic benefit.

- Study 005 also showed statistically significant effects on increasing total ON time without troublesome dyskinesia and on decrease total OFF time by the primary ANOVA analyses and that these changes in opposite directions were of a similar magnitude of approximately 1 hour.

- Changes in UPDRS Part II (ADL) and in UPDRS Part III (motor subscale) were small and not statistically significant by the primary ANOVA analysis. Neither was the Clinical Global Impression of Improvement (CGI-I) scoring statistically significant for indicating a global impression of clinical improvement.

- Overall, I interpret all these diary based results as "positive" and supporting efficacy of istradefylline for the 40 mg dose in this trial conducted in North America (U.S. and Canada).

Study 006 (North America)

Reviewer Comment(s)

- In Study 006, 20 mg istradefylline showed a smaller decrease (-3.65 %) on the mean treatment difference (vs placebo) for the change from baseline of percentage of daily awake time OFF than the respective decrease (-6.78 %) in Study 005 and this small decrease was not statistically significant by the primary, prespecified statistical analysis (ANOVA). A statistically significant effect for a larger decrease was observed only when an alternative, statistical analysis (ANCOVA), which was considered "supportive," was applied.

- Neither was the increase (+3.89 %) in percentage of daily awake ON time without troublesome dyskinesia (important corresponding efficacy endpoint to the primary efficacy endpoint) statistically significant for 20 mg istradefylline by the primary pre-specified ANOVA analysis. The "supportive" alternative statistical analysis (ANCOVA)

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was not statistically significant for important endpoint. This increase by the primary analysis was also notably less than the increase (+5.60 %) observed in Study 005.

- The decrease in total OFF hours was quite small (- 0.39 hours) and not statistically significant for the 20 mg dose according to the primary ANOVA analysis. Although an increase in total ON time without troublesome dyskinesia was statistically significant by the primary ANOVA analysis, an increase in this endpoint by the alternative ANCOVA analysis or MMRM analysis was not statistically significant suggesting that the ANOVA result was not very robust. It is not clear why there was such a large difference in the increase (+ 0.93 hours) for ON and the decrease (-0.39 hours) in OFF.

- Changes in UPDRS Part II (ADL) and in UPDRS Part III (motor subscale) were small and not statistically significant by the primary ANOVA analysis for 20 mg istradefylline. Neither was the Clinical Global Impression of Improvement (CGI-I) scoring statistically significant indicating a global impression of clinical improvement.

- For completeness sake, I will also review results for the 60 mg istradefylline dose in this only pivotal study which investigated this larger dose that the sponsor does not proposed to market. The 60 mg istradefylline showed a relatively small decrease (- 3.77 %) in the change from baseline of percentage of daily awake time OFF. This decrease was similar to the small decrease (- 3.65 %) of the much lower dose (20 mg) in the same trial. This small decrease was not statistically significant by the primary, prespecified statistical analysis (ANOVA). A statistically significant effect for a somewhat larger decrease (- 4.49 %) was observed only when an alternative, statistical analysis (ANCOVA), which was considered "supportive," was applied.

- A relatively small increase (+ 3.55 %, and smaller than the + 3.89 % increase for 20 mg in the same study) in percentage of daily awake ON time without troublesome dyskinesia (important corresponding efficacy endpoint to the primary efficacy endpoint) was statistically significant for 60 mg istradefylline by the primary pre-specified ANOVA analysis. Neither was the result for the "supportive" alternative statistical analysis (ANCOVA) statistically significant for important endpoint. The increase for 60 mg was also notably less than the increase (+5.60 %) observed in Study 005.

- A modest decrease in total OFF hours (- 0.55 hours) was not statistically significant for the 60 mg dose according to the primary ANOVA analysis or alternative ANCOVA analysis Similarly, the increase in total ON time without troublesome dyskinesia was not statistically significant by the primary ANOVA analysis or alternative ANCOVA analysis.

- Changes in UPDRS Part II (ADL) and in UPDRS Part III (motor subscale) ranged from being absent to relatively small and were not statistically significant by the primary ANOVA analysis for either istradefylline dose. Neither was the Clinical Global

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Impression of Improvement (CGI-I) scoring statistically significant for indicating a global impression of clinical improvement.

- Overall, I interpret all these diary based results as "negative" for supporting efficacy of istradefylline for the 20 mg dose (or even 60 mg dose) in this trial conducted in North America (U.S. and Canada). The sponsor considers this trial as "positive" for supporting efficacy of 20 mg istradefylline based simply upon showing a statistically significant effect of the primary efficacy endpoint with an alternative, "supportive" analysis (ANCOVA). Importantly, the sponsor disregards :1) the primary efficacy endpoint results of the ANOVA analysis which had been prespecified as the primary statistical analysis for this trial; and 2) also the facts that istradefylline did not produce a statistically significant increase in percentage of ON time without troublesome dyskinesia (by ANOVA or ANCOVA), the important corresponding endpoint to the primary endpoint which can indicate a direct therapeutic benefit. I disagree with the sponsor's perspective on this trial based upon my outlined interpretations of results in this trial.

Study 013 (U.S.)

Reviewer Comment(s)

- In Study 013, 20 mg istradefylline was associated with a statistically significant decrease (- 4.57 %) on the mean treatment difference (vs placebo) for the primary efficacy endpoint of change from baseline for percentage of daily awake OFF time by the primary, pre-specified statistical analysis ANCOVA. This result was not statistically significant by the MMRM analysis suggesting lack of robustness, The treatment difference by the primary analysis was also notably lower than the effect on the same endpoint in Study 005.

- Istradefylline (20 mg) did not show a statistically significant benefit on percentage of ON of daily awake time without troublesome dyskinesia, the critically important corresponding efficacy endpoint to the primary efficacy endpoint which can show a direct therapeutic benefit to the patient.

- Istradefylline (20 mg) did not show a statistically significant increase for the important efficacy endpoint of ON time without troublesome dyskinesia by the primary analysis. Although 20 mg was associated with a statistically significant effect by the primary analysis for decrease in total OFF time, the result by the MMRM analysis was not statistically significant suggesting lack of robustness for the primary analysis result, nor for the corresponding total hours change for change from baseline of OFF time,

- Changes in UPDRS Part II (ADL) and in UPDRS Part III (motor subscale) were minimal or relatively small and not statistically significant by the primary ANCOVA analysis.

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Neither was the Clinical Global Impression of Improvement (CGI-I) scoring statistically significant for indicating a global impression of clinical improvement.

- I consider Study 013 conducted only in the U.S. for investigating efficacy of 20 mg istradefylline as a "negative" study because several other important diary based efficacy endpoint were not statistically significant in support of efficacy of this istradefylline dose.

Study 018 (North America)

Reviewer Comment(s)

- In Study 018, no doses (10 mg, 20 mg, 40 mg) of istradefylline produced a statistically significant decrease on the mean treatment difference (vs placebo) on the primary efficacy endpoint of change from baseline for percentage of daily OFF time. In fact, the effect of the 10 mg and 20 mg doses were positive (+1.79 % for 10 mg; + 1.50 % for 20 mg) indicating a mean numerical worsening effect on this endpoint for istradefylline. The effect of the highest 40 mg dose was minimal (- 0.66 %) and did not suggest any appreciable benefit on this endpoint.

- There was no statistically significant effect of any of the three doses (10 mg, 20 mg. 40 mg). Similarly as for the primary efficacy endpoint, all 3 doses of istradefylline were associated with a mean numerical worsening result relative to the desired effect for the critically important corresponding efficacy endpoint (to the primary efficacy endpoint) of change of percentage of daily awake ON time without troublesome dyskinesia.

- All three doses (10 mg, 20 mg, 40 mg) showed a mean numerical worsening effect (i.e., negative change) for the important efficacy endpoint of change from baseline for total ON hours without troublesome dyskinesia. The effect on the corresponding diary based endpoint of change from baseline in total OFF time/hours was similarly not suggestive in the least for any efficacy, The 10 mg and 20 mg doses were associated with a numerical worsening effect on the endpoint for total OFF time hour and the 40 mg dose show an effect (- 0,03 hours) close to 0 for this endpoint.

- Treatment difference for change in UPDRS Part II (ADL) was minimal or absent for all 3 doses and not statistically significant. Treatment difference for the highest dose (40 mg) was associated with a statistically significant decrease (- 2.1) for change in UPDRS Part III (motor subscale), but treatment differences for a decrease for the lower doses (10 mg, 20 mg) were minimal or absent and not statistically significant. It is not possible to say whether the effect for the 40 mg dose was by chance. by the primary ANOVA analysis for 60 mg istradefylline. The Clinical Global Impression of Improvement (CGI-I) scoring indicating a global impression of clinical improvement was not statistically significant. All doses for CGI-I were associated with very high p values ranging from 0,564,to 0.953.

- Overall, I consider results from Study 018 to be extremely negative and not supportive of efficacy for a wide range of doses (10 mg, 20 mg, and 40 mg) in the same study in which

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large numbers of patients (nearly 150 per treatment group) had been studied in potentially relevant populations in the U.S. and Canada. In more than 20 years of experience of reviewing and evaluating drugs for Parkinson's disease, I cannot ever recall seeing such a large study of a wide range of doses with such negative results most of which actually suggest a numerical worsening of the desired effect of the drug. My concern and skepticism of efficacy for istradefylline is particularly targeted for the absence of any suggestion of efficacy/benefit for the highest dose 40 mg which the sponsor has proposed to be marketed in the U.S. The sponsor has not provided any possible explanations nor speculation for the complete lack of suggestion of efficacy in this large, important trial.

Study 007 (Europe, South America, Asia, South Africa)

Reviewer Comment(s)

- In Study 007, 40 mg istradefylline was associated with a minimal effect (- 0.61 %) on the mean treatment difference (vs placebo) on the primary efficacy endpoint, percentage change of daily awake OFF time, which was not only not statistically significant (P=0.729) but was extremely far from a statistically significant value of P<0.05 in this predominantly Caucasian patients from various locations outside of the U.S.. This result clearly did not suggest any efficacy of this dose of istradefylline. The reviews for the original submission and non-approvable letter to the sponsor identified the important observation that a “positive” control arm for entacapone was nearly statistically significant for this primary efficacy endpoint.

- The istradefylline effect on the mean treatment difference (vs placebo) for the important efficacy endpoint (corresponding to the primary efficacy endpoint), change from baseline for percentage of daily awake ON time without troublesome dyskinesia (which can indicate direct therapeutic benefit), was minimal (- 0.66 %) with a similarly very high P value (P=0.646) for statistical significance.

- There was no suggestion of any efficacy of 40 mg istradefylline on important efficacy endpoints of change from baseline in OFF time and in ON time without troublesome dyskinesia Results from this trial argue against expected efficacy of the maximally proposed dose of istradefylline (40 mg) to be marketed in a diverse racial population of Parkinson's disease patients in the U.S.

- Istradefylline effects on mean treatment difference for other important efficacy endpoints showed no appreciable effects on change from baseline for total ON hours without troublesome dyskinesia (- 0.01 hours, technically a minimally worsening numerical point estimate but really representing a 0 effect) and no appreciable effect on change from baseline for total OFF hours (-0.07 hours or – 4 minutes).

- Changes in UPDRS Part II (ADL) and in UPDRS Part III (motor subscale) were minimal or relatively small not statistically significant by the primary ANCOVA analysis for 40 mg istradefylline. Neither was the Clinical Global Impression of Improvement (CGI-I)

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scoring statistically significant for indicating a global impression of clinical improvement.

- Overall, I interpret this trial to be extremely negative and not supportive in the least for the highest proposed dose (40 mg) which the sponsor has proposed to be marketed. The observation that a positive control was close to showing statistically significant therapeutic benefit further underscores my skepticism of efficacy of istradefylline.

Study 0608 (Japan)

Reviewer Comment(s)

- Treatment differences for both istradefylline doses (20 mg, 40 mg) were associated with statistically significant results for the primary efficacy endpoint, change from baseline in total OFF hours according to the primary statistical analysis.

- Although the 40 mg dose was associated with a statistically significant effect on the important efficacy endpoint (i.e., change from baseline in total ON hours without troublesome dyskinesia) showing a direct therapeutic benefit, the 20 mg did not produce a statistically significant effect on this important endpoint based upon the primary analysis. However, the MMRM analysis for this endpoint was not statistically significant for the 40 mg dose suggesting that the primary analysis result was not very robust,

- Along these same lines as noted above for changes in total OFF hours and total ON hours without troublesome dyskinesia, the primary statistical analysis showed a statistically significant effect for both doses for change of the percentage of daily awake time as OFF. However, the primary statistical analyses did not show statistically significant effects on the corresponding endpoint (percentage change of daily ON time without troublesome dyskinesia) associated with a direct therapeutic benefit to patients.

- Treatment difference for a change in UPDRS Part III (motor subscale) for both doses showed a statistically significant decrease by the primary ANCOVA analysis for 60 mg istradefylline. Neither was the Clinical Global Impression of Improvement (CGI-I) scoring statistically significant for indicating a global impression of clinical improvement.

- Changes in UPDRS Part II (ADL) and in UPDRS Part III (motor subscale) were minimal and not statistically significant. by the primary ANOVA analysis for 60 mg istradefylline. Neither was the Clinical Global Impression of Improvement (CGI-I) scoring statistically significant for indicating a global impression of clinical improvement.

- Overall, I consider this trial to be a "positive" trial for showing efficacy of istradefylline in this Japanese population. Although results for the 40 mg dose is positive for the primary efficacy endpoint of decreasing OFF time and corresponding important endpoint

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of increasing ON time without troublesome dyskinesia, the results for efficacy of 20 mg was not as strong. My concern with the 20 mg dose rests with the inability of this dose to show a statistically significant effect on the important endpoints of increase of total ON time without troublesome dyskinesia and an increase in the percentage of awake time for this endpoint according to the primary analysis.

Study 009 (Japan)

Reviewer Comment(s)

- Treatment differences for both istradefylline doses (20 mg, 40 mg) were associated with statistically significant results for the primary efficacy endpoint, change from baseline in total OFF hours according to the primary statistical analysis.

- Both doses were also associated with a statistically significant effect on the important efficacy endpoint (i.e., change from baseline in total ON hours without troublesome dyskinesia) showing an increase in this endpoint and a direct therapeutic benefit.

- Both of these doses also showed statistically significant effects on change for both corresponding percentage endpoints (i.e., decrease of percentage daily awake OFF time and increase of percentage daily ON time without troublesome dyskinesia according to the primary analysis.

- Treatment difference for a change in UPDRS Part III (motor subscale) was statistically significant for 40 mg but was not statistically significant for the 20 mg which was associated with much smaller effect according to the primary analysis. The effect of both doses on change in UPDRS Part II-ADL absent or minimal for both dose. Of interest, Clinical Global Impression of Improvement (CGI-I) scoring was statistically significant for indicating a global impression of clinical improvement for both doses. Considering all the different doses in all 8 pivotal trials, this trial was the only one in which a statistically significant benefit was observed for this global assessment of improvement.

- Overall, considering results for all the efficacy endpoints upon which I have focused, this pivotal trial in Japan was the most supportive of all 8 pivotal trials for efficacy of istradefylline for both doses (20 mg, 40 mg). I will address my concerns about the applicability of results from this trial to the U,S, population in the section on my Integrated Assessment of Effectiveness. It is also important to recognize that overall there was no clear dose-response for these doses because results for both doses for all diary based efficacy endpoints were always similar. In some instances, the numerical treatment difference was greater for the 20 mg dose than that of the 40 mg dose.

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Study 014 (North America, Europe, Israel)

Reviewer Comment(s)

- There was no statistically significant effect on the treatment difference for both doses (20 mg, 40 mg) for the primary efficacy endpoint, change from baseline in total OFF hours according to the primary MMRM analysis. The treatment difference for both doses was small (~ -0.3 hours) but similar. This important study, for which planning in close conjunction with the DNP began in 2012, was designed specifically to address DNP concerns about efficacy of istradefylline identified in original NDA submission.

- Neither was there a statistically significant effect on the important efficacy endpoint, change from baseline in total ON hours without troublesome dyskinesia, which can show direct therapeutic benefit to patients for either dose. Most importantly, the treatment difference for the highest dose (40 mg) for this endpoint was 0 with a P value of almost 1 (P=0.986). This result is extremely concerning to me considering that this complete absence of any benefit for the 40 mg dose considering that this is the third time (also in Studies 018 and EU-07) that NO benefit was observed for the 40 mg for this most important efficacy endpoint to me. I reiterate that I believe that it is extremely rare to observe essentially a 0 effect for this important efficacy endpoint in a pivotal for patients with advanced Parkinson's disease.

- There was no statistically significant effect for the treatment difference for either dose for the change from baseline in UPDRS Part II-ADL and UPDRS-Part III. In addition, CGI-I scoring as an impression of global improvement was not statistically significant for either dose. Of note, the P value for the 40 mg dose was very high (P=0.872).

- Overall, results of this study, which had been planned to meet DNP expectations/recommendations for demonstrating efficacy of istradefylline was clearly "negative" and did not achieve the objective of this pivotal trial to demonstrate efficacy of istradefylline to the Agency.

7.1.2. Subpopulations/Subgroups

The sponsor conducted various subgroup/subpopulation analyses for efficacy for the two Japanese studies (0608, 009) but did not present specific results for each subgroup. instead the sponsor presented results regarding whether there was a statistical interaction for the subgroup.

The following tables show binary subgroup analyses for age, weight, and sex for the treatment difference (vs placebo) for each dose for the primary efficacy endpoint of change from baseline for OFF hours in each Japanese trial. These subgroup analyses were conducted by Dr. Ling, the primary statistical reviewer. There was no subgroup analyses for race because all patients were Japanese.

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Table 56 Subgroup Analyses for Treatment Difference (Istradefylline – Placebo) for Change from Baseline in Total OFF Hours According to Age, Weight, and Sex in Study 0608 (Conducted by Dr. Ling, Primary Statistical Reviewer)

	Analysis Group	Istradefylline 20 mg/day	Istradefylline 40 mg/day
		Difference from Placebo hours (95% CI)	Difference from Placebo hours (95% CI)
Age			
	<65 years (n=170)	-1.02 (-1.84, -0.20)	-0.69 (-1.46, 0.08)
	>=65 years (n=187)	-0.42 (-1.25, 0.42)	-1.10 (-1.96, -0.23)
Weight			
	<55 kg (n=188)	-0.88 (-1.69, -0.07)	-1.23 (-2.04, -0.41)
	>=55 kg (n=169)	-0.34 (-1.29, 0.60)	-0.21 (-1.14, 0.73)
Sex			
	Female (n=207)	-0.82 (-1.60, -0.03)	-1.05 (-1.82, -0.28)
	Male (n=150)	-0.26 (-1.24, 0.71)	-0.32 (-1.29, 0.65)

*ANCOVA OC

Table 57 Subgroup Analyses for Treatment Difference (Istradefylline – Placebo) for Change from Baseline in Total OFF Hours According to Age, Weight, and Sex in Study 009 (Conducted by Dr. Ling, Primary Statistical Reviewer)

	Analysis Group	Istradefylline 20 mg/day	Istradefylline 40 mg/day
		Difference from Placebo hours (95% CI)	Difference from Placebo hours (95% CI)
Age			
	<65 years (n=149)	-0.45 (-1.35, 0.46)	-0.24 (-1.17, 0.70)
	>=65 years (n=217)	-0.85 (-1.62, -0.09)	-1.28 (-2.01, -0.54)
Weight			
	<55 kg (n=185)	-0.67 (-1.42, 0.08)	-0.92 (-1.69, -0.14)
	>=55 kg (n=181)	-1.23 (-2.11, 0.35)	-0.65 (-1.51, 0.21)
Sex			
	Female (n=204)	-1.06 (-1.71, -0.42)	-0.97 (-1.69, -0.26)
	Male (n=162)	-0.41 (-1.52, 0.70)	-0.94 (-1.93, 0.54)

*ANCOVA OC

Reviewer Comment(s)

- In Table 56 and Table 57 there appeared to be some marked differences in the mean treatment difference for the primary efficacy endpoint for some subgroups depending on the istradefylline dose and the specific Japanese trial and whether the treatment difference

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was statistically significant. I will comment only when a subgroup difference suggests consistency for the nature of the difference for both doses in both trials.

- The treatment difference for females appeared to be notably much greater than that for males for both doses in Study 0608 but only for 20 mg istradefylline in Study 009. Although the treatment difference was technically larger for females for the 40 mg dose in Study 009, this difference was minimal. In the ISE, the sponsor noted that the pool for all trials for females vs males was much greater for the primary efficacy endpoint in females. However, when the sponsor showed female vs male results for each of the individual pivotal trials, a notably greater treatment difference for female vs male did not appear to be a consistent observation in each of the 8 pivotal trials.

- Regarding a binary cut-off for weight (55 kg; post-hoc analysis), the treatment difference was notably greater for patients < 55 kg for both doses in Study 0608 and also for the 40 mg dose in Study 009. However, the ≥ 55 kg subgroup showed a greater effect for the 20 mg dose in Study 009.

- Regarding a binary cut-off for age (65 years), the treatment difference was notably greater for patients ≥ 65 years for both doses in Study 009 and also for the 40 mg dose in Study 0608. However, the < 65 year subgroup showed a greater effect for the 20 mg dose in Study 009.

Geographic Regional Subgroup/Subpopulation Analyses

The sponsor conducted subgroup analyses for the treatment difference for change for ON time without troublesome dyskinesia and for change for OFF time in pools of patients in the two Japanese pivotal trials and in the six pivotal trials conducted outside of Japan in assessing a geographic regional subgroup effect. Figure 3 through Figure 6 show efficacy results for these endpoints for both doses in trials conducted in Japan vs outside of Japan according to both MMRM and ANCOVA statistical analyses.

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Figure 3 **Difference in LS Means [95% C.I.] (vs. placebo), Change from Baseline at Week 12 Total hours of ON Time Without Troublesome Dyskinesia MMRM Model - Observed Case Analysis - mITT Analysis Set; Pool All Pivotal Trials**

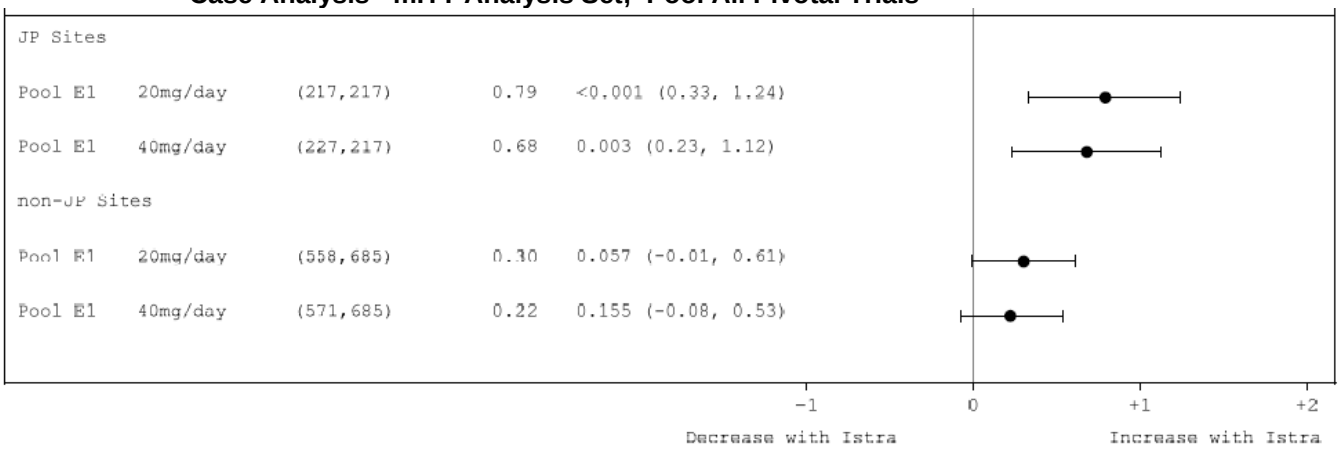
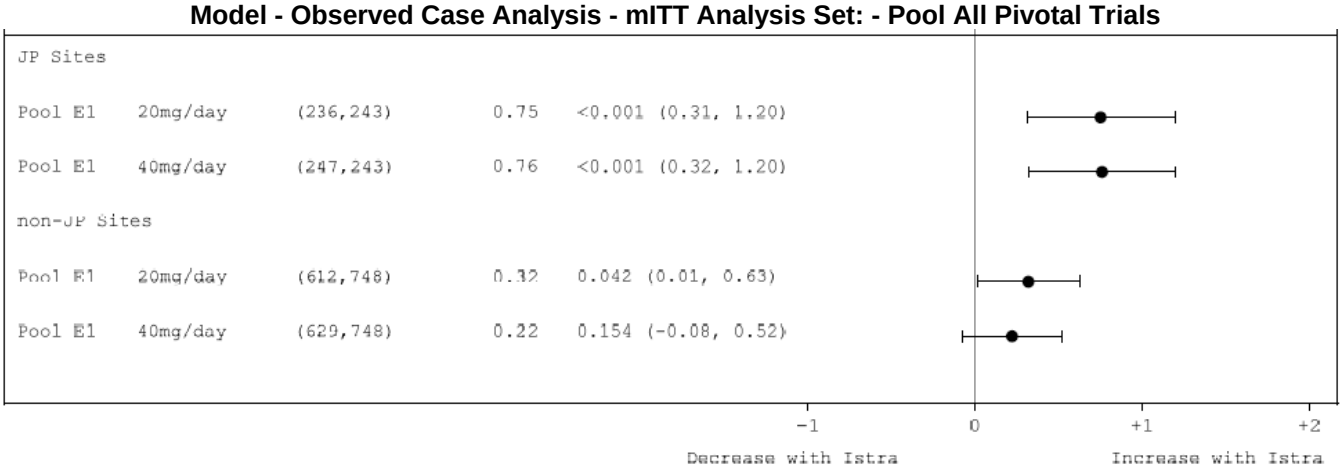


Figure 4 **Difference in LS Means [95% C.I.] (vs. placebo), Change from Baseline at Week 12 Total hours of ON Time Without Troublesome Dyskinesia ANCOVA with LOCF Model - Observed Case Analysis - mITT Analysis Set: - Pool All Pivotal Trials**



Reviewer Comment(s)

- Figure 3 shows that the mean treatment difference (vs placebo) for the 20 mg dose and 40 mg dose was much smaller (62 % lower for 20 mg and 68 % lower for 40 mg) in the pool for 6 pivotal trials outside of Japan compared to the pool of Japanese pivotal trials for the important efficacy endpoint of change for ON time without troublesome dyskinesia according to the MMRM analysis. Whereas results for both doses were statistically significant for the Japanese trials, results for the outside of Japan trials were not statistically significant.

- Figure 4 (above) shows essentially similar results for the ANCOVA analyses as was observed in Figure 3 in the MMRM analyses. More specifically, the mean treatment difference (vs placebo) for the 20 mg dose and 40 mg dose was much smaller (57 % lower for 20 mg and 71 % lower for 40 mg) in the pool for 6 pivotal trials outside of Japan compared to the pool of Japanese pivotal trials for the important efficacy endpoint of change for ON time without troublesome dyskinesia. Whereas results for both doses

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were statistically significant for the Japanese trials, results for the outside of Japan trials were not statistically significant for the 40 mg dose but was barely statistically significant for the 20 mg dose.

Figure 5 **Difference in LS Means [95% C.I.] (vs. placebo), Change from Baseline at Week 12 Total hours of OFF Time MMRM Model - Observed Case Analysis- mITT Analysis Set; Pool All Pivotal Trials**

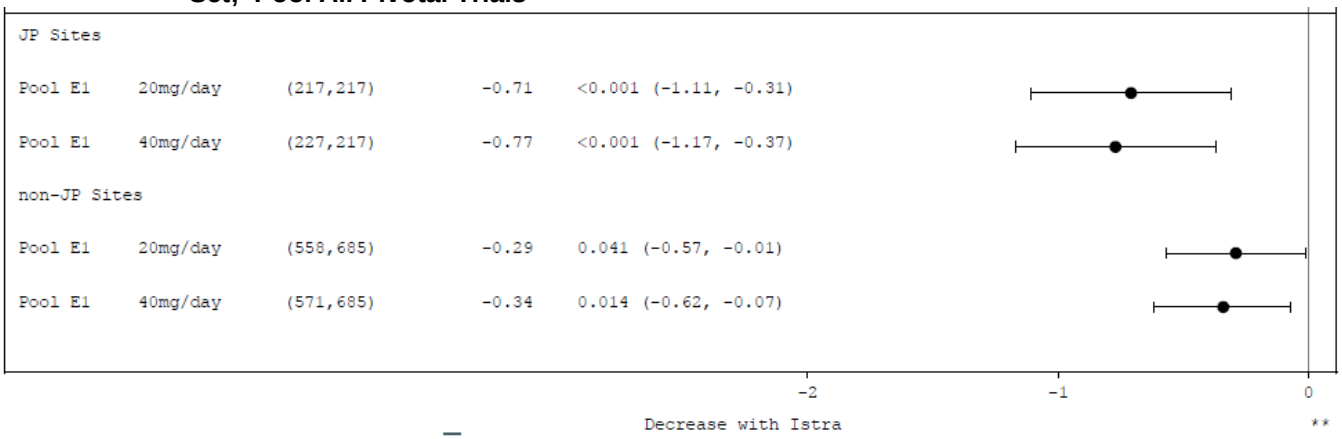
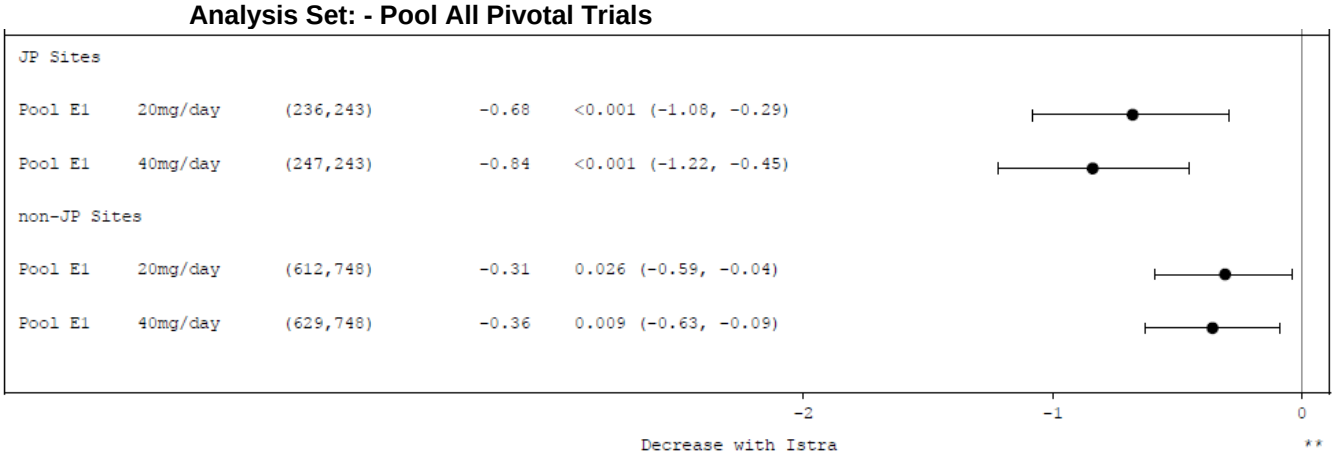


Figure 6 **Difference in LS Means [95% C.I.] (vs. placebo), Change from Baseline at Week 12 Total hours of OFF Time ANCOVA with LOCF Model - Observed Analysis - mITT Analysis Set: - Pool All Pivotal Trials**



Reviewer Comment(s)

- Figure 5 shows that the mean treatment difference (vs placebo) for the 20 mg dose and 40 mg dose was much smaller (63 % lower for 20 mg and 56 % lower for 40 mg) in the pool for 6 pivotal trials outside of Japan compared to the pool of Japanese pivotal trials for the primary efficacy endpoint of change for OFF time. Although results for both regional subgroups were statistically significant, the level of statistical significance was much stronger for the Japanese trials compared to the level of statistical significance for the pivotal outside of Japan.

  Figure 6 shows essentially similar results for the ANCOVA analyses as was observed in Figure 5 in the MMRM analyses. More specifically, the mean treatment difference (vs placebo) for the 20 mg dose and 40 mg dose was much smaller (54 % lower for 20 mg

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and 57 % lower for 40 mg) in the pool for 6 pivotal trials outside of Japan compared to the pool of Japanese pivotal trials for the primary efficacy endpoint of change for OFF time. Although results for both regional subgroups were statistically significant, the level of statistical significance was much stronger for the Japanese trials compared to the level of statistical significance for the pivotal outside of Japan.

Weight-Based Subgroup/Subpopulation Post-Hoc Analyses

During the review, in attempting to ascertain whether there might be any noteworthy differences in the Japanese patients vs the non-Japanese patients it was noted that there were very large weight differences in the patients in the Japanese pivotal trials (mean/median weight ~ 55 kg) compared to the pivotal trials outside of Japan (mean/median weight ranged from ~ 70 – 80 kg). Initially, the sponsor was asked to conduct weight-based analyses based upon several binary cut-off thresholds (i.e., 50, 65, 80, 95 kg) for what I considered as the most important efficacy endpoints (change from baseline for ON time without troublesome dyskinesia and for OFF time).

The sponsor provided the following description of the models for the MMRM and ANCOVA statistical analyses:

- Difference in LS means, 95% CI and p-value are from paired comparisons between each istradefylline treatment arm vs placebo. A mixed model repeated measures approach was used with baseline assessment as a covariate, and study, study center nested within study, treatment group, week, and treatment-by-week interaction as fixed effect terms

- Difference in LS means, 95% CI and p-value are from paired comparisons between each istradefylline treatment arm vs placebo. An ANCOVA model was used with baseline assessment as a covariate, and study, study center nested within study and treatment group as fixed effect terms.

The following tables show results of these and additional weight based analyses. These summary tables were created by the Clinical Reviewer based upon tables provided by the sponsor in response to my information requests.

Table 58 shows efficacy results for change from baseline for the treatment difference of ON time without troublesome dyskinesia and of OFF time for various subgroups based upon binary (below or equal to/above) specific weight thresholds (50, 65, 80, 95 kg) in all 8 pivotal trials according to MMRM and ANCOVA statistical analyses. Yellow highlight also indicates when the result was not statistically significant ($p > 0.05$).

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Table 58 **Comparison of Change from Baseline of Important Efficacy Endpoints on Istradefylline Treatment Difference (Istradefylline 20 mg or 40 mg – Placebo) in Pivotal Trial Pools Relative to Binary Weight Thresholds According to MMRM and ANCOVA (with LOCF) Statistical Analyses**

Endpoint	< 50 kg				≥ 50 kg				< 65 kg				≥ 65 kg			
	Istradefylline 20 mg		Istradefylline 40 mg		Istradefylline 20 mg		Istradefylline 40 mg		Istradefylline 20 mg		Istradefylline 40 mg		Istradefyline 20 mg		Istradefyline 40 mg	
	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA
Total Daily ON Hours WO Troublesome Dyskinesia	+0.90 P=0.021 (Istra-92, Plac-107)	+0.93 P=0.023 (Istra-101, Plac-119)	+0.35 P=0.361 (Istra-92, Plac-107)	+0.55 P=0.182 (Istra-101, Plac-119)	+0.39 P=0.006 (Istra-683, Plac-793)	+0.41 P=0.004 (Istra-747, Plac-870)	+0.33 P=0.019 (Istra-706, Plac-793)	+0.34 P=0.015 (Istra-775, Plac-793)	+0.70 P=0.001 (Istra-298, Plac-341)	+0.62 P=0.005 (Istra-328, Plac-380)	+0.60 P=0.004 (Istra-302, Plac-341)	+0.61 P=0.004 (Istra-336, Plac-380)	+0.28 P=0.101 (Istra-477, Plac-559)	+0.29 P=0.088 (Istra-520, Plac-609)	+0.20 P=0.238 (Istra-496, Plac-559)	+0.18 P=0.296 (Istra-540, Plac-609)
Total Daily OFF Hours	-0.78 P=0.018 (Istra-92, Plac-107)	-0.80 P=0.019 (Istra-101, Plac-119)	-0.81 P=0.013 (Istra-92, Plac-107)	-0.83 P=0.014 (Istra-101, Plac-119)	-0.37 P=0.004 (Istra-683, Plac-793)	-0.37 P=0.001 (Istra-747, Plac-870)	-0.41 P=0.001 (Istra-706, Plac-9793	-0.42 P=<0.001 (Istra-775, Plac-870)	-0.53 P=0.006 (Istra-298, Plac-341)	-0.51 P=0.012 (Istra-328, Plac-380)	-0.63 P=<0.001 (Istra-302, Plac-341)	-0.66 P=<0.001 (Istra-336, Plac-380)	-0.27 P=0.080 (Istra-477, Plac-559)	-0.30 P=0.055 (Istra-520, Plac-609)	-0.30 P=0.051 (Istra-496, Plac-559)	-0.33 P=0.034 (Istra-540, Plac-609)

Yellow highlight indicates NOT STATISTICALLY SIGNIFICANT

Istra = Istradefylline N; Plac = Placebo N

Endpoint	< 80 kg				≥ 80 kg				< 95 kg				≥ 95 kg			
	Istradefyline 20 mg		Istradefyline 40 mg		Istradefyline 20 mg		Istradefyline 40 mg		Istradefyline 20 mg		Istradefyline 40 mg		Istradefyline 20 mg		Istradefyline 40 mg	
	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA	MMRM	ANCOVA
Total Daily ON Hours WO Troublesome Dyskinesia	+0.48 P=0.002 (Istra-508, Plac-589)	+0.47 P=0.003 (Istra-558, Plac-652)	+0.40 P=0.008 (Istra-508, Plac-589)	+0.44 P=0.004 (Istra-608, Plac-652)	+0.33 P=0.167 (Istra-267, Plac-311)	+0.32 P=0.183 (Istra-290, Plac-337)	+0.17 P=0.503 (Istra-249, Plac-311)	+0.06 P=0.817 (Istra-268, Plac-337)	+0.43 P=0.002 (Istra-676, Plac-793)	+0.45 P=<0.001 (Istra-744, Plac-873)	+0.35 P=0.010 (Istra-705, Plac-793)	+0.40 P=0.002 (Istra-775, Plac-873)	+0.27 P=0.562 (Istra-99, Plac-107)	+0.42 P=0.406 (Istra-104, Plac-116)	+0.51 P=0.297 (Istra-93, Plac-107)	+0.52 P=0.333 (Istra-101, Plac-116)
Total Daily OFF Hours	-0.51 P=0.<001 (Istra-508, Plac-589)	-0.57 P=0.<001 (Istra-558, Plac-652)	-0.57 P=0<.001 (Istra-549, Plac-589)	-0.63 P=<0.001 (Istra-608, Plac-652)	-0.11 P=0.596 (Istra-267, Plac-311)	-0.13 P=0.541 (Istra-290, Plac-337)	-0.15 P=0.499 (Istra-249, Plac-311)	-0.15 P=0.519 (Istra-268, Plac-337)	-0.36 P=0.004 (Istra-676, Plac-793)	-0.36 P=0.003 (Istra-744, Plac-873)	-0.46 P=<0.001 (Istra-705, Plac-793)	-0.53 P=<0.001 (Istra-775, Plac-873)	-0.34 P=0.440 (Istra-99, Plac-107)	-0.37 P=0.416 (Istra-104, Plac-116)	-0.63 P=0.174 (Istra-93, Plac-107)	-0.62 P=0.205 (Istra-101, Plac-116)

Yellow highlight indicates NOT STATISTICALLY SIGNIFICANT

Istra = Istradefylline N; Plac = Placebo N

Reviewer Comment(s)

- All patients in each less than weight category for each binary weight threshold cut-off were associated with efficacy results for both endpoints (ON without troublesome dyskinesia and OFF) which were statistically significant ($p < 0.05$). In contrast, all patients in the greater than or equal weight category for 65 kg, 80 kg, and 95 kg were associated with efficacy results for both endpoints (ON without troublesome dyskinesia and OFF) which were not statistically significant despite the fact that results were based upon large number of patients.

- Mean treatment difference results for the 20 mg and 40 mg istradefylline doses were consistently smaller in the ≥ 65 kg, and ≥ 80 kg categories than in the < 65 kg, , and < 80 kg categories for both efficacy endpoints (ON without troublesome dyskinesia and OFF) according to both statistical analyses. The only exception to this pattern was in the ≥ 95 kg category which was composed of relatively small numbers (~ 100) of patients in the placebo and istradefylline groups and which were much smaller than the numbers of patients in the ≥ 65 kg, and ≥ 80 kg categories.

- Overall, I interpreted these results as suggesting the possibility that efficacy results were related to weight and that heavier patients experience potentially much lower efficacy from istradefylline. These results prompted me to request additional weight-based analyses in which patients were in mutually exclusive weight categories. The following tables will show such results.

Table 59 shows efficacy results for the mean treatment difference for important efficacy endpoints (change from baseline for ON time without troublesome dyskinesia and for OFF time) based upon various mutually exclusive weight categories (< 55 kg, ≥ 55 kg - < 70 kg, ≥ 70 kg - < 85 kg, ≥ 85 kg) according to MMR and ANCOVA statistical analyses in pools of patients from all 8 pivotal trials. The number of patients (i.e., N) in each separate weight subgroup category for placebo/istradefylline was quite large as shown in Table 59.

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Table 59 **Treatment Difference (Istradefylline – Placebo) in Pools of All 8 Pivotal Trials Analyzed According to Mutually Exclusive Weight Categories, Istradefylline Dose, and Statistical Analysis (MMRM and ANCOVA with LOCF) (YELLOW HIGHLIGHT INDICATES NOT STATISTICALLY SIGNIFICANT, P>0.05)**

Endpoint	Least Square Mean (LSM) Treatment Difference (Istradefylline – Placebo) (N for Placebo, N for Istradefylline) P Value															
	MMRM Statistical Analysis								ANCOVA with LOCF							
	20 MG				40 MG				20 MG				40 MG			
	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg
CFB Total ON Hours WO TD	+0.77 (173, 140) P=0.012	+0.51 (250, 234) P=0.054	+0.22 (258, 197) P=0.385	+0.21 (219, 204) P=0.474	+0.69 (173, 153) P=0.020	+0.35 (250, 237) P=0.171	+0.09 (258, 223) P=0.721	-0.09 (219, 185) P=0.776)	+0.81 (195, 158) P=0.010	+0.65 (278, 250) P=0.018	+0.24 (280, 220) P=0.385	+0.21 (236, 220) P=0.501	+0.77 (195, 175) P=0.013	+0.32 (278, 259) P=0.226	+0.18 (280, 243) P=0.489	-0.30 (236, 199) P=0.381
CFB Total OFF Hours	- 0.61 (173, 140) P=0.021	-0.52 (250, 234) P=0.026	-0.31 (258, 197) P=0.193	+0.02 (219, 204) P=0.951	-0.84 (173, 153) P=0.001)	-0.38 (250, 237) P=0.095	-0.44 (258, 223) P=0.058	+0.07 (219, 185) P=0.814	-0.66 (195, 158) P=0.013	-0.53 (278, 250) P=0.030	-0.25 (280, 220) P=0.311	+0.02 (236, 220) P=0.931	-0.88 (195, 175) P<0.001	-0.41 (278, 259) P=0.076	-0.47 (280, 243) P=0.052	+0.15 (236, 199) P=0.592

Summary table created by Reviewer Len Kapcala based upon sponsor conducted analyses from information request
20 mg Istradefylline dose investigated in Studies 006-NA, 013-US, 018-NA, 608-JAP, 009-JAP, 014-US/EU/Is
40 mg Istradefylline dose investigated in Studies 005-NA, 018-NA, 007-EU/SA/AS/SAF, 608-JAP, 009-JAP, 014-US/EU/Is
CFB = Change from Baseline; WO TD = Without Troublesome Dyskinesia
Red font indicates numerical worsening effect on efficacy endpoint or minimal, numerical, positive effect (i.e., less than 0.1 hour or 6 minutes)

Reviewer Comment(s)

- There was a progressive decrease across each weight category for the mean treatment difference for change for OFF time for 20 mg istradefylline as weight increases according to both statistical analyses.

- There was a progressive decrease of OFF time for the 40 mg dose as weight increased considering that the point estimate of the treatment difference was a similar effect for the 55 - < 70 kg and 70 – < 85 kg parts (i.e., 55 - < 85 kg) of the dose-response curve.

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- There was a complete loss of any numerical efficacy for the change for OFF time in patients in the ≥ 85 kg category. In each of these categories for both endpoints and both analyses, the mean numerical treatment difference was surprisingly in the opposite direction as desired for efficacy and was consistent with numerical worsening for each efficacy endpoint.

- There was a progressive decrease of the increase in ON time without troublesome dyskinesia for the 20 mg dose as weight increased (considering an essentially similar effect on the 70 - < 85 kg and > 85 kg categories on the dose response curve) according to both analyses.

- There was a progressive decrease of the increase of ON time without troublesome dyskinesia for the 40 mg dose as weight increases according to both statistical analyses.

- There was a complete loss of any numerical efficacy for increase of ON without troublesome dyskinesia for 40 mg in patients with a weight of ≥ 85 kg according to both statistical analyses. The numerical treatment difference in this category was the surprisingly with the opposite sign of what was desired suggesting a worsening effect on the endpoint.

The following tables/analyses show efficacy results for the mutually exclusive weight-based categories for both important efficacy endpoints according to geographic regional analyses of important efficacy endpoints (change of ON time without troublesome dyskinesia and of OFF time) and also according to both statistical analyses.

Table 60 shows the istradefylline treatment difference for change from baseline of ON time without troublesome dyskinesia and of OFF time for both istradefylline doses according to various, mutually exclusive baseline weight categories in a pool of patient in Japanese pivotal trials (0608, 009) compared to a pool of pivotal trials outside of Japan (005, 006, 007, 013, 014, 018). These results were analyzed by an MMTM statistical analysis. Table 61 shows the same information according to an ANCOVA statistical analysis.

Table 60 **Treatment Difference (Istradefylline – Placebo) in Pools of All 8 Pivotal Trials Analyzed According to Mutually Exclusive Weight Categories, Istradefylline Dose, in Different Geographic Regions (Japan vs Outside of Japan and Statistical with MMRM Statistical Analysis (YELLOW HIGHLIGHT INDICATES NOT STATISTICALLY SIGNIFICANT, P>0.05)**

Endpoint	Least Square Mean (LSM) Treatment Difference (Istradefylline – Placebo) (N for Placebo, N for Istradefylline) P Value															
	20 MG								40 MG							
	Japan				Outside of Japan				Japan				Outside of Japan			
	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg
CFB Total ON Hours WO TD	+0.83 (120, 112) P=0.010	+0.64 (78, 89) P=0.085	+0.74 (16, 15) P=0.271	-1.82 (3, 1) P=0.689	+0.32 (53, 28) P=0.563	+0.52 (172, 145) P=0.086	+0.40 (242, 182) P=0.102	+0.20 (216, 203) P=0.476	+0.82 (120, 108 P=0.012	+0.58 (78, 92) P=0.119	+0.39 (16, 21) P=0.524	+1.07 (3, 6) P=0.696	+0.51 (53, 45) P=0.296	+0.44 (172, 145) P=0.148	+0.12 (242, 202) P=0.601	-0.07 (216, 179) P=0.803
CFB Total OFF Hours	- 0.73 (120, 112) P=0.008	-0.71 (78, 89) P=0.045	-0.63 (16, 15) P=0.354	+1.47 (3, 1) P=0.666	-0.62 (53, 28) P=0.298	-0.51 (172, 145) P=0.046	-0.51 (242, 182) P=0.022	-0.06 (216, 203) P=0.827	-1.03 (120, 108) P<0.001	-0.66 (78, 92) P=0.059	-0.46 (16, 21) P=0.464	+0.57 (3, 6) P=0.773	-0.83 (53, 45) P=0.113	-0.44 (172, 145) P=0.086	-0.35 (242, 202) P=0.107	-0.05 (216, 179) P=0.859

Summary table created by Reviewer Len Kapcala based upon sponsor conducted analyses from information request
20 mg Istradefylline dose investigated in Studies 006-NA, 013-US, 018-NA, 608-JAP, 009-JAP, 014-US/EU/Is
40 mg Istradefylline dose investigated in Studies 005-NA, 018-NA, 007-EU/SA/AS/SAF, 608-JAP, 009-JAP, 014-US/EU/Is
CFB = Change from Baseline; WO TD = Without Troublesome Dyskinesia
Red font indicates numerical worsening effect on efficacy endpoint or minimal, numerical, positive effect (i.e., less than 0.1 hour or 6 minutes)

Reviewer Comment(s)

- It is not clear whether there is any pattern of change foe the 20 mg dose in the Japanese trials for the lowest 3 weight categories. The highest category ≥ 85 kg only has one istradefylline treated patient and even the next lowest category has only 15 istradefylline patients, Based upon my review of the 2 lowest weight categories which consists of most of the patients treated, the mean treatment difference for ON time without troublesome dyskinesia and for OFF seem relatively similar.

- Regarding the 40 mg dose in the Japanese trials, most of the patients are contained in the 2 lowest weight categories similarly as for the 20 mg dose, The mean treatment difference for the ≥ 55 kg - < 70 kg is greater than that for the lowest category

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- (< 55 kg) for ON time without troublesome dyskinesia and also for OFF time. Despite the fact the higher weight category consists of a relatively large number of patients (92 istradefylline, 76 placebo) neither result is statistically significant but the p values seem to be trending toward statistical significance.

- Regarding the patients in the pivotal trials outside of Japan, the vast majority of patients are distributed in the 3 highest weight categories. Because he number of istradefylline-treated patients in the lowest weight category is relatively small (28 for 20 mg and 45 for 40 mg), the mean value for both doses does not seem reliable for comparing to each of the other 3 categories each of which consists of approximately 150 to 200 istradefylline-treated patients for the 20 mg and 40 mg doses.

- For the 20 mg dose, there is a progressive decrease in the mean treatment difference for ON time without troublesome dyskinesia across the 3 highest weight categories in patients outside of Japan and none of the mean treatment differences are associated with a statistically significant p value despite such large numbers of patients in the istradefylline and placebo groups for each category. For OFF time, the treatment difference for the $\geq$ 55 kg - < 70 kg and the $\geq$ 70 kg - < 85 kg category is similar but the treatment difference for the highest weight category ($\geq$ 85 kg) is approaching 0 (- 0.06). These results suggest substantial effects of weight for affecting treatment response.

- For the 40 mg dose, there is a progressive decrease in the mean treatment difference for ON time without troublesome dyskinesia across all 4 weight categories in patients outside of Japan and none of the mean treatment differences are associated with a statistically significant p value despite such large numbers of patients in the istradefylline and placebo groups for each category. For OFF time, the treatment difference for each of the 4 categories is similarly progressively lower as the weight category increases. Of significant increase, the mean treatment difference for ON time without troublesome dyskinesia and for OFF time is numerically a small value in the opposite direction expected for a benefit and thus technically suggesting a small numerical worsening effect for each of the important endpoints. Furthermore, the p value for each endpoint is very high 0.803 and 0.859.t. These results strongly raise the question that efficacy is diminished and potentially lost depending on the weight of the patient in the trials outside of Japan.

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Table 61 **Treatment Difference (Istradefylline – Placebo) in Pools of Pivotal Trials Analyzed According to Mutually Exclusive Weight Categories for Istradefylline Dose in Different Geographical Regions (Japan vs Outside of Japan) with ANCOVA (with LOCF) Statistical Analysis (YELLOW HIGHLIGHT INDICATES NOT STATISTICALLY SIGNIFICANT, P>0.05)**

Endpoint	Least Square Mean (LSM) Treatment Difference (Istradefylline – Placebo) (N for Placebo, N for Istradefylline) P Value															
	20 MG								40 MG							
	Japan				Outside of Japan				Japan				Outside of Japan			
	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg	< 55 Kg	≥ 55 – < 70 Kg	≥ 70 – < 85 Kg	≥ 85 Kg
CFB Total ON Hours WO TD	+0.79 (132, 122) P=0.013	+0.57 (87, 97) P=0.113	+0.97 (21, 16) P=0.125	-6.05 (3, 1) P=0.198	+0.17 (63, 36) P=0.749	+0.50 (191, 153) P=0.091	+0.40 (259, 204) P=0.090	+0.21 (233, 219) P=0.446	+0.87 (132, 120) P=0.006	+0.63 (87, 99) P=0.079	+0.66 (21, 22) P=0.257	+1.91 (3, 6) P=0.426	+0.42 (63, 55) P=0.372	+0.42 (191, 160) P=0.148	+0.21 (259, 221) P=0.364	-0.17 (233, 193) P=0.542
CFB Total OFF Hours	- 0.71 (132, 122) P=0.008	-0.66 (87, 97) P=0.051	-0.72 (21, 16) P=0.267	+6.13 (3, 1) P=0.208	-0.56 (63, 36) P=0.294	-0.53 (191, 153) P=0.042	-0.55 (259, 204) P=0.013	-0.06 (233, 219) P=0.815	-1.06 (132, 120) P<0.001	-0.70 (87, 99) P=0.037	-0.60 (21, 22) P=0.313	+0.99 (3, 6) P=0.599	-0.77 (63, 55) P<0.098	-0.52 (191, 160) P=0.044	-0.49 (259, 221) P=0.022	+0.03 (233, 193) P=0.894

Summary table created by Reviewer Len Kapcala based upon sponsor conducted analyses from information request
20 mg Istradefylline dose investigated in Studies 006-NA, 013-US, 018-NA, 608-JAP, 009-JAP, 014-US/EU/Is
40 mg Istradefylline dose investigated in Studies 005-NA, 018-NA, 007-EU/SA/AS/SAF, 608-JAP, 009-JAP, 014-US/EU/Is
CFB = Change from Baseline; WO TD = Without Troublesome Dyskinesia
Red font indicates numerical worsening effect on efficacy endpoint or minimal, numerical, positive effect (i.e., less than 0.1 hour or 6 minutes)

Reviewer Comment(s)

- Overall, results in Table 61 with the ANCOVA were similar to those shown in Table 60 with the MMRM analysis. I will comment on a few differences which I consider to be relatively minor and not substantive.

- I consider the results and my interpretations of them for the trials conducted in Japan to be similar to the results and interpretations outlined for the MMRM analyses.

- For the 20 mg analyses for patients in trials outside of Japan, I consider the results and my comments to be similar those for the MMRM analyses.

- For the 40 mg analyses for patients in trials outside of Japan, the differences across the 4 individual weight subgroups did not seem as apparent as they seemed to be in the MMRM analyses. Regarding a change in ON time without troublesome

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dyskinesia, the increase for the two lowest weight subgroups were similar (up to < 70 kg), and then decreased notably for each higher weight subgroup. Regarding a change in OFF time, the largest decrease was in the lowest weight group (< 55 kg), then the decrease for the two middle weight subgroups was smaller than that that for the lowest weight subgroup but were similar for the combined category(≥ 55 kg - < 85 kg). The change for OFF in the highest weight subgroup (≥ 85 kg) was much less than that for all lower weight subgroups and was actually a mean numerical change that was positive, suggesting a worsening of OFF time.

- Overall, I consider the MMRM and ANCOVA analyses as clearly suggesting that : 1) efficacy (based upon change of ON time without troublesome dyskinesia and change of OFF time) notably, and progressively decreases for patients outside of Japan as weight increases for the 20 gm and 40 mg doses; and 2) efficacy can completely disappear for the subgroup of heaviest patients (≥ 85 kg/187 lbs). The FDA Clinical Pharmacology team conducted specific analyses for these 4 weight categories and concluded that pharmacokinetic (PK) exposure data do not support a possible explanation for these observations because istradefylline exposure is not decreased in heavier patients as weight increases.

7.1.3. Dose and Dose-Response

During the original NDA review, the Clinical Team did not think that there was evidence for dose-response across many doses ranging between 10 mg and 60 mg daily in the 5 pivotal trials which had been reviewed. Overall, results from both Japanese trials do not suggest a dose-response between the 20 mg and 40 mg dose. Although occasionally, a greater effect was observed for an efficacy endpoint at the 40 mg dose compared to the 20 mg dose. However, most commonly, results were similar for both doses and not infrequently, the result for the 20 mg dose was numerically greater than that for the 40 mg dose. Furthermore, exposure-response analyses did not support dose-response.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

In response to a request from the DNP at the Pre-NDA meeting, the sponsor provided analyses for efficacy of the endpoints over time. My review of these analyses for OFF time or ON time without troublesome dyskinesia of the 3 trials (Study 005 and 2 Japanese trials: 0608 and009) I consider as being overall "positive" for efficacy suggest that efficacy was often apparent as early as 2 weeks after treatment and in general was similar to the efficacy at the end of the trial (e.g., at 12 weeks).

7.2. Additional Efficacy Considerations

I have presented my efficacy considerations which I consider important and relevant.

7.2.1. Considerations on Benefit in the Postmarket Setting

NA

7.2.2. Other Relevant Benefits

No comment.

7.3. Integrated Assessment of Effectiveness

Table 62 consisting of post-hoc analyses which I have conducted shows percentage of patients in the 8 pivotal trials according to my overall conclusion as to whether I considered the individual trial as being : 1) "negative" because it did not demonstrate efficacy of istradefylline; 2) "equivocal" because it may have showed some evidence for istradefylline efficacy but this evidence was considered to be weak and/or inconsistent across important endpoints; and 3) "positive" because it did demonstrate istradefylline evidence.

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Table 62 Percentage of Istradefylline-Treated Patients in Pivotal Trials with Negative Efficacy, Equivocal Efficacy, and Positive Efficacy Relative to All Pivotal Trials or to Defined Regional Pivotal Trials

Study Population	% Istradefylline Patients for 10 mg	% Istradefylline Patients for 20 mg	% Istradefylline Patients for 40 mg	% Istradefylline Patients for 60 mg
# Patients in 3 Negative Efficacy Trials (007,014,018)/ # Patients in All Trials	149/149 (100 %)	338/848 (40 %)	503/879 (57 %)	NA
# Patients in 3 Negative Efficacy Trials (007,014,018)/ # Patients in All Trials Outside of Japan	149/149 (100 %)	338/613 (55 %)	503/632 (80 %)	NA
# Patients in 2 Equivocal Efficacy Trials (006,013)/ # Patients in All Trials	NA	275/848 (32 %)	NA	155/155 (100 %)
# Patients in 2 Equivocal Efficacy Trials (006,013)/ # Patients in All Trials Outside of Japan	NA	275/613 (45 %)	NA	155/155 (100 %)
# Patients Who Are NOT in Positive Efficacy Trials (007, 014,018,006,013)/ # Patients in All Trials	NA	613/848 (72 %)	503/879 (57 %)	NA
# Patients Who Are NOT in Positive Efficacy Trials (007, 014,018,006,013)/ # Patients in All Trials Outside of Japan	NA	613/613 (100 %)	503/632 (80 %)	NA
# Patients in 3 Positive Trials (005,0608,009)/ # Patients in All Trials	NA	235/848 (28 %)	376/879 (43 %)	NA
# Patients in 3 Positive Trials (005,0608,009)/ # Patients in All Trials Outside of Japan	NA	NA	129/632 (20 %)	NA
# Patients in 2 Positive Japanese Trials (0608,009)/ # Patients in All Trials	NA	235/848 (28 %)	247/879 (28 %)	NA

Negative Efficacy Trials (007, 014, 018) assessed by Clinical Reviewer (Dr. Kapcala)
Equivocal Efficacy Trials (006, 013) assessed by Clinical Reviewer (Dr. Kapcala)
Positive Efficacy Trials (005, 0608, 009) assessed by Clinical Reviewer (Dr. Kapcala)
# Patients in cells derived from data in ISE Table 2.1-1
NA=Not Applicable
Analyses conducted by Clinical Reviewer

Reviewer Comment(s)

- Table 62 helps provides quantitative insight into the numbers of patients who had been treated with istradefylline (10 mg, 20 mg, 40 mg, 60 mg daily doses) in all 8 pivotal trials and I had considered/categorized the trial as negative for efficacy, equivocal for efficacy or positive for efficacy. The percentage of patients in a category is shown relative to the total number of all patients treated with istradefylline for a specific dose and also relative to the total number of all patients treated with istradefylline for a specific dose outside of Japan. These analyses also provide insight into the relative contribution of the trials consisting of only Japanese patients.

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- Regarding the 40 mg dose, 57 % of all patients treated with that dose were in a negative trial which did not show efficacy and 80 % were in a negative trial considering only trials outside of Japan. A relatively small percentage (43 %) of all patients treated with that dose were in a positive trial relative to all trials and only 20 % were in a positive trials considering only trials outside of Japan.

- Regarding the 20 mg dose, 40 % of all patients treated with that dose were in a negative trial which did not show efficacy and 55 % were in a negative trial considering only trials outside of Japan. A relatively small percentage (28 %) of all patients treated with that dose were in a positive trial relative to all trials and these were the trials consisting solely of Japanese patients. If one considers the percentage of 20 mg patients who were not in a positive trial, that percentage (72 %) is quite high for all trials and even higher (100 %) when considering all trials which were not positive relative to trials outside of Japan.

- Regarding the 60 mg dose, 100 % of the patients were in equivocal trials which showed weak/inconsistent efficacy relative to all patients in all trials and relative to trials outside of Japan.

- Regarding the 10 mg dose, 100 % of the patients were in a negative trial which did not show efficacy relative to all patients in all trials and relative to trials outside of Japan.

- Overall, Table 62 strongly supports the impression that most positive results supporting efficacy of istradefylline are derived from the Japanese trials for the 40 mg dose and that all positive results supporting efficacy for 20 gm are derived solely from the Japanese trials.

Reviewer Comments for Integrated Assessment of Effectiveness

- Table 54 and Table 55 comprehensively show results for many efficacy endpoints of interest for each of the pivotal trials according to the pre-specified statistical analysis and also for the MMRM analysis which was an alternate analysis for all trials except for Study 014 (where it was the primary analysis) applied to show how robust results might be. My comments immediately following those tables are fairly detailed.

  In this section, I will summarize my main comments for results in these tables, The vast majority of results are concordant for showing statistical significant ($p < 0.05$) or not showing statistical significant ($p > 0.05$) by the primary, pre-specified analysis and by the MMRM analysis (the important analysis determined for Study 014 and analyses in the ISE). Yellow highlighting emphasize results which are not statistically significant. The vast majority of results are not statistically significant. Whereas some results are clearly negative regardless of what is assessed. Some results might show a statistically significant effect for the primary efficacy related to an OFF assessment but frequently, the corresponding endpoint for ON without troublesome dyskinesia (which I consider as the most important efficacy endpoint for showing a real benefit to the patient) is not statistically significant. In some instances, lack of robustness is observed because the

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MMRM analysis is not statistically significant. Percentages shown in Table 62 also support the view that most of the efficacy data from 8 pivotal trials are not positive for supporting istradefylline efficacy and that the bulk of support comes primarily from the Japanese trials. Although results from Japanese Study 009 seems clearly positive, results from Japanese Study 0608 are associated with some concerns/caveats, such as not showing statistical significance for the 20 mg dose for increasing ON without troublesome dyskinesia by any analysis and by not showing robustness for this effect for the 40 mg dose because this result is not statistically significant by the MMRM analysis.

Despite the fact that 8 pivotal trials are adequate and well-controlled, it is difficult to dismiss the overwhelming negative data from the other 5 pivotal trials which consists of large percentages of istradefylline treated patients and also that 5 of 6 pivotal trials conducted outside of Japan are not positive for demonstrating efficacy.

- When the DNP met with the sponsor on 12/2/12, I attended that meeting. At that time we knew about the efficacy results of both Japanese trials (0608 and 009) but yet Study 014 was planned to address DNP concerns about the weak and inconsistent efficacy of the 5 pivotal trials originally submitted in the NDA. If the results of the Japanese trials were sufficient for resubmitting the NDA with those trials, it does not seem logical that the sponsor would have wanted to conduct Study 014 and that the DNP would have encouraged the sponsor to conduct Study 014 in a population who had been "optimally" treated. I also note that I had the perspective back in 2012 that the Japanese trials were not adequate to support an NDA and still have that perspective.

  Although I consider Study 009 as the stronger study of the these two conducted in Japan, I have concluded that Study 0608 can also be considered to be "positive" but with some concerns/caveats suggesting that results are not clearly robust. I am unable to consider that all the new supporting data are from Japanese adequate for supporting approval of the NDA when the vast majority of previous efficacy data outside of Japan were considered weak/inconsistent. Furthermore, I am troubled by the fact that the sponsor cannot exclude the possibility that overall the best istradefylline efficacy results as a whole come from Japanese trials (and not trials outside of Japan) because Japanese patients have a genetic/racially based sensitivity/responsiveness to istradefylline. The sponsor had not addressed this possibility when arguing for the generalizability of the Japanese results.

- Study 014 was planned by the sponsor with the DNP to address previously outlined concerns and to attempt to show a benefit of istradefylline in patients who were "optimally" treated. The FDA agreed with the design of this study and issued a Special Protocol Assessment (SPA) acknowledging its agreement. However, results from this key study did not allay DNP concerns but only served to heighten them regarding the question of istradefylline efficacy. This trial (conducted in the U.S., Canada, Europe and Israel) was the largest of all pivotal trials and enrolled nearly 200 patients per arm for placebo, 20 mg and 40 mg. Results for 20 mg and 40 mg were not statistically significant for the primary efficacy endpoint with a small numerical effect and p values which were

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not trending toward statistical significance. Whereas both doses did not show any statistically significant benefit on what I consider the most important endpoint (ON without troublesome dyskinesia) for indicating a direct therapeutic benefit. What was most concerning was the fact that the treatment difference for this important efficacy endpoint for the 40 mg dose was 0 and the corresponding p value was nearly 1. Overall, results from this study heightened efficacy concerns which were initially identified in the original NDA submission, and further raised questions about the ability observed significant efficacy from istradefylline in patients outside of Japan.

- I do not agree with the possible explanations offered by the applicant for the negative results obtained in 3 large pivotal trials (Studies 018, 007, 014) in which large numbers of patients outside of Japan were studied and for which the results for the primary efficacy endpoint are either very weak or suggesting a worsening effect on OFF (i.e., Study 018). Furthermore, the change of the important efficacy endpoint of ON time without troublesome dyskinesia is essentially 0 for all 3 trials (with p values approaching 1 and ranging between 0.929 to 0.986) for the 40 mg dose which is the highest dose the sponsor would like to market. In my 20 years of experience with drugs for Parkinson's disease, I cannot recall ever seeing a drug (which was ultimately approved by FDA) with such weak efficacy in so many large, pivotal trials.

- I am further troubled and skeptical about the efficacy of istradefylline based upon the subgroup/subpopulation efficacy results I have presented based upon various weight analyses of subgroups. These results raise the questions that patients outside of Japan experiencing decreasing istradefylline efficacy as weight increases and that some "heavier" patients might not experience any efficacy from istradefylline. A possible explanation seems like it must be on pharmacodynamic basis because istradefylline exposure does not decrease as weight increases. This concern about the potential effect of weight could be studied prospectively in a randomized, double-blinded, placebo-controlled pivotal trial.

  It is interesting that overall the best efficacy results were obtained in the 2 pivotal studies conducted in Japan compared to overall efficacy results of the 6 pivotal studies conducted outside of Japan and that the weight of patients in the studies in Japan (mean/median weight ~ 55 kg) was much lower than the weight of patients in trials outside of Japan (mean/median weight ~ 70 – 80 kg).

- Given all my concerns which I have summarized here and outlined in more detail in other sections of my review, I am unable to conclude there is substantial evidence for the effectiveness of istradefylline and am not confident that istradefylline will have the effect purported to have in the label for patients in the U.S. in accordance with 21CFR 314.125 as shown below here.

Under 21CFR 314.125, one reason not to approve an NDA:
(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it

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purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

I also share the concerns which had been outlined previous by the Agency regarding the potential for no benefit or a weak effect of istradefylline. If patients used istradefylline and experienced no benefit or weak effects instead of another clearly effective adjunctive treatment, they could expose themselves to a serious risk such as a fall resulting in a hip fracture with potentially associated serious consequences on morbidity and even mortality.

8. Review of Safety

Not Applicable for this section and all following subsections.

I did not review the safety of istradefylline. The safety of istradefylline was reviewed by Dr. Natalie Branagan. Refer to her review regarding the safety review of istradefylline for this NDA re-submission.

8.1. Safety Review Approach

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Sample Table A: Safety Population, Size, and Denominators [Replace this title with a Table

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Caption using the *Insert Caption* button in the CRT tab.]

Safety Database for the Study Drug[1] Individuals exposed to any treatment in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Healthy volunteers			
Controlled trials conducted for this indication[2]			
All other trials conducted for this indication[3]			
Controlled trials conducted for other indications[4]			

[1] *Study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] If placebo arm patients switch to study drug in open label extension, then the sample n should count those patients only once; do not count twice patients who go into extension from randomized study drug arm
[4] Include n in this row only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review.

Sample Table B. Duration of Exposure [Replace this title with a Table Caption using the *Insert Caption* button in the CRT tab.]

	Number of patients exposed to the study drug:				
Dosage	>= 1 dose	>=6 months[1]	>=12 months	>=18 months	18 months or longer
Dose 1	N=	N=	N=	N=	N=
Dose 2, etc.	N=	N=	N=	N=	N=

[1] These time interviews are provided as a sample. Time interval and cumulative treatment duration selected for this table will vary among products and should be based on experience with a specific product under review

8.2.2. Relevant characteristics of the safety population:

8.2.3. Adequacy of the safety database:

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

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8.3.2. Categorization of Adverse Events

8.3.3. Routine Clinical Tests

8.4. Safety Results

8.4.1. Deaths

8.4.2. Serious Adverse Events

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

8.4.4. Significant Adverse Events

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

8.4.6. Laboratory Findings

8.4.7. Vital Signs

8.4.8. Electrocardiograms (ECGs)

8.4.9. QT

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8.4.10. Immunogenicity

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. [Name Safety Issue]

8.6. Safety Analyses by Demographic Subgroups

8.7. Specific Safety Studies/Clinical Trials

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

8.8.2. Human Reproduction and Pregnancy

8.8.3. Pediatrics and Assessment of Effects on Growth

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

8.9.2. Expectations on Safety in the Postmarket Setting

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8.9.3. Additional Safety Issues From Other Disciplines

8.10. Integrated Assessment of Safety

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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My following comments for the istradefylline label, which the DNP is revising, pertain to section 14 (Clinical Studies).

- Only describe results of studies (005, 013, 0608, 009) which were statistically significant for the primary efficacy endpoint according to the pre-specified statistical analysis as per the plan by the DNP.
- Describe effects on the endpoint for ON without troublesome dyskinesia which corresponds to the primary efficacy (change of percentage OFF or total hours OFF).
- Delete details about other adjunctive Parkinson's disease treatments
- Delete the figure showing istradefylline effects over time

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

12. Postmarketing Requirements and Commitments

Because I am recommending against approval of istradefylline, I do not have any recommendations for postmarketing requirements or commitments.

13. Appendices

13.1. References

13.2. Financial Disclosure

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Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: _____201 Principal Investigators; 821 Subinvestigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ 0 Significant payments of other sorts: _____ 0 Proprietary interest in the product tested held by investigator: _____ 0 Significant equity interest held by investigator in S 1 Sponsor of covered study: _____ 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐ X	No ☐ (Request explanation from Applicant)

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LEONARD P KAPCALA
08/27/2019 10:23:09 AM
Dave, ready for your signature. Thanx. Len

GERALD D PODSKALNY
08/27/2019 10:25:33 AM

MEMORANDUM

DATE: February 25, 2008

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-075

SUBJECT: Divisional Recommendation for Action on NDA 22-075, for the use of Istradefylline Tablets in the treatment of Advanced Parkinson's Disease

NDA 22-075, for the use of Istradefylline Tablets, an adenosine A2A receptor antagonist, in the treatment of Advanced Parkinson's Disease, was submitted on March 29, 2007 by Kyowa Pharmaceuticals, Inc. The presumed mechanism of action of this drug is quite complicated and explained in detail in the clinical review, but briefly, the anti-PD effect presumably arises secondary to a net inhibitory effect on neural pathways that leads to a decrease in inhibitory influences in the thalamus and cerebral cortex. The application contains reports of five randomized controlled trials, three of which are submitted by the sponsor as establishing substantial evidence of effectiveness for istradefylline for the proposed indication. The application has been reviewed by Dr. Gerald Podskalny, medical officer, Dr. Ohidul Siddiqui, statistician, Drs. John Duan and Venkatesh Atul Bhattaram, Office of Clinical Pharmacology, Dr. Terrie Peters, pharmacology reviewer, Dr. Lois Freed, pharmacology team leader, Dr. Wendy Wilson, chemist, Dr. Steve Thomson, statistics (carcinogenicity), Dr. Denise V. Baugh, Division of Medication Errors and Technical Support, and Dr. Norman Hershkowitz, acting clinical team leader. The clinical team has concluded that the application should not be approved, and Dr. Siddiqui considers the data equivocal. In this memo, I will briefly summarize the relevant evidence of safety and effectiveness, and offer the division's recommendation for action on the NDA.

Effectiveness

As noted above, the sponsor has submitted results for five controlled trials. The studies were essentially identical in design, with minor variations in duration, and with varying doses. The studies were randomized, multi-center, placebo controlled trials in which patients were randomized to either one or several fixed doses of istradefylline or placebo. The primary outcome in all studies was the change from baseline in the percentage of waking hours spent in the OFF state. Multiple secondary outcome measures were assessed in each study.

The three studies considered to provide substantial evidence of effectiveness by the sponsor were all performed in the US, each of which was 12 weeks in

duration; Study 005 (Pbo, 40mg), Study 006 (Pbo, 20 and 60 mg), and Study 013 (Pbo, 20mg). The other two studies were Study EU-007 (Pbo, 40mg, Entacapone; 16 weeks) and Study US-018 (Pbo, 10mg, 20mg, and 40mg). The following table displays the results on the primary outcome measure in the five controlled studies.

CHANGE FROM BASELINE IN PERCENT WAKING TIME SPENT OFF

Study	Placebo	20mg	40mg	60mg	Entacapone
005	-4.04% (N=66)		-10.81% (N=129) p=0.007		
006	-4.07% (N=77)	-7.72% (N=163) p=0.026		-7.84% (N=155) p=0.024	
013	-4.92% (N=113)	-9.49% (N=112) p=0.025			
018*	-8.31% (N =146)	-6.81% (N=144) p=0.41	-8.97% (N=145) p=0.71		
EU-007	-4.53% (N=151)		-5.14% (N=158) p=0.73		-7.82% (N=146) p=0.064

* results of the 10mg group (similar to that for the 20mg group) not shown
p-values are compared to placebo

Secondary Outcomes

As noted above, each study included multiple secondary outcome measures, many of which were common to all of the studies. The following secondary outcomes were assessed (as change from baseline) in each of these studies:

UPDRS Parts I-III or I-IV (ON and OFF)
CGI

PGI (patient-rated global rating; Studies 013, 018, 007;)
SF-36 (only in Study 013)
PDQ-39 (Studies 018 and 007)
Percentage of Wake Time ON without dyskinesia
Percentage of Wake Time ON with dyskinesia
Percentage of Wake Time ON with non-troublesome dyskinesia
Percentage of Wake Time ON with troublesome dyskinesia

There were no nominally statistically significant between-group differences in any of these outcomes, with the exception of an increase in the change from baseline on drug compared to placebo in the percentage (p=0.047) and total (p=0.035) hours of Wake Time with dyskinesia in Study 005.

The sponsor also described another study, Study 051, in which patients were randomized to either istradefylline 40 mg (N=94) or placebo (N=82) as monotherapy (early Parkinson's Disease). The primary outcome in this study was Part III (motor score) of the UPDRS. This was a 12 week study; the p-value for the contrast on the primary outcome was p=0.23. The PGI and all other secondary outcomes (e.g., other UPDRS sub-scales, CGI, Timed Tapping Test) were also assessed in this study; no between-treatment contrasts reached statistical significance.

Another trial, Study 0406, was performed in 13 centers in Japan. In this study, patients were randomized to Placebo (N=30), istradefylline 20 mg (N=31) or 40 mg (N=28). Although this study was obviously small and underpowered, the following results were obtained on the Change from Baseline in the Percent of Wake Time in the OFF State:

Drug	Change	P-value vs Placebo
Placebo	-8.23	
Istradefylline 20mg	-4.83	0.5
Istradefylline 40mg	-7.66	0.94

SAFETY

A total of 1264 patients received a dose of either 40mg or 60mg/day for at least 6 months, and 371 patients received either dose for at least one year, for a total of 1279 patient-years of exposure at either of these 2 doses. A total of 1737 patients received either of these 2 doses in either controlled and/or open-label conditions, with 1663 patients receiving any dose of istradefylline in controlled trials.

Deaths

In controlled trials, there were 2.2 deaths/100 patient-yrs of exposure in placebo patients, and 1.2 deaths/100 patient-years in all istradefylline-treated patients. In open-label exposure, there were between 0.4-0.8 deaths/100 patient-years. The causes of the deaths in istradefylline-treated patients did not appear obviously drug-related.

Serious ADRs

In controlled trials of PD, a total of 4.4% of istradefylline-treated and 3.4% of placebo-treated patients experienced a serious adverse reaction. The only SAR that occurred more than twice in any istradefylline dose group was Accident, which occurred in 0.9% (N=4) of the istradefylline 40mg/day group compared to 0.2% (N=1) placebo-treated patients. In controlled trials of any indication, a total of 3.5% of istradefylline-treated patients experienced an SAR compared to 2.6% of placebo patients. The only SAR that occurred more than twice in any istradefylline dose group was Accident, which occurred in 0.5 % (N=4) of the istradefylline 40mg/day group compared to 0.1% (N=1) placebo-treated patients.

Discontinuations

In controlled trials of PD, 6% of istradefylline-treated patients and placebo-treated patients withdrew due to an ADR. However, the following discontinuation rates by dose were seen:

Dose	Rate of D/C
Placebo	6.06
Istra 10mg	3.27
Istra 20mg	6.09
Istra 40mg	7.27
Istra 60mg	10.32

The following table displays those ADRs associated with discontinuations in controlled trials of PD that occurred in more than one patient in any istradefylline dose group:

ADR	Placebo	10mg	20mg	40mg	60mg
Chest pain	0	0	0	2	0
Dyskinesia	3	0	2	6	7
Increased LFTs	1	0	1	2	2
Muscle Rigidity	1	0	1	2	0
Nausea	1	1	1	2	4
PD	8	1	3	2	1

Other ADRs

The following ADRs appeared to be clearly drug-related:

ADR	Placebo	10mg	20mg	40mg	60mg
Nausea	6.6%	7.1%	8.9%	7.9%	22.6%
Dyskinesia	13.3%	21.3%	21.3%	23.1%	23.9%
Abn'l dreams	0.5%	3.2%	2.6%	1.6%	5.2%
Constipation	3.7%	6.5%	7.7%	6.3%	1.9%
Hallucination	2.7%	1.3%	3.0%	3.6%	5.8%
Confusional State	0.4%	3.2%	1.2%	0.7%	1.3%

Impulsive behaviors

Dopaminergic drugs have been associated with impulsive and compulsive behaviors (uncontrolled urges to gamble, have sex, or other compulsive behaviors). Although reports of these behaviors were not specifically solicited, in controlled trials, 2 istradefylline patients experienced compulsive gambling (both at 20mg/day), 2 istradefylline patients experienced other compulsive behaviors, and 3 istradefylline patients experienced some variant of hypersexuality (none in PD studies). No such cases were reported in placebo patients.

In long-term open-label studies in PD, there were 14 patients with reports of hypersexuality (13 at 40mg/day, 1 at 60mg/day) and 9 patients with compulsive gambling (8 at 40mg/day, 1 at 60 mg/day).

Laboratory Testing

There were no clinically meaningful mean changes in any specific laboratory measure, nor were there important increases in istradefylline-treated patients who met criteria for clinically significant changes. However, more istradefylline-treated patients had lab values shift from normal to abnormal than placebo patients for the following tests:

INCREASE FROM NORMAL TO HIGH

Dose	SGPT	SGOT	T. Bili	LDH
Placebo	6%	5%	4.3%	6.6%
Istra 10	5.2%	6%	2.6%	7.8%
Istra 20	5%	4%	3.5%	8.7%
Istra 40	8.4%	9.4%	6.4%	10.3%
Istra 60	10.4%	13.6%	6.5%	10.4%

Open-label data did not reveal any meaningful changes otherwise.

One subject in a controlled trial receiving istradefylline 40mg/day experienced a "sudden elevation of amylase, lipase, and trypsin-like immunoreactivity…" and then died, according to Dr. Podskalny. The death was not attributed to pancreatitis, although there was no obvious reason to exclude this as a cause (or contributory factor).

Four subjects were discontinued from PD controlled trials because of elevated LFTs.

A 44 year old man receiving istradefylline 60mg/day experienced an increase in ALT, AST, LDH, CPK, and T.Bili noted on Day 56 of treatment. The CPK was noted to have been elevated a month earlier (about 2 X ULN) and peaked at about 30 X ULN. The AST peaked at about 4 X ULN, and T.Bili at about 3 X ULN (the patient's baseline T. Bili was also about 3 X ULN, and had "dropped" to about 2 X ULN before peaking at Day 84). The drug was discontinued on Day 58, and the abnormal labs returned to normal several days later.

Another patient was withdrawn from istradefylline 20mg/day on Day 57 because of ALT/AST of 2-3 X ULN. Another was withdrawn on Day 15 because of ALT/AST 4 X ULN. A third was withdrawn from istradefylline 20mg/day after 2 weeks because of AST 4 X ULN. In the latter 2 cases, the LFTs were slightly elevated at baseline. All three cases resolved off drug.

There were no systematic abnormalities on vital signs or EKG. An adequately designed and conducted thorough QT study evaluated a maximum dose of 160mg/day, and noted no important changes.

Other Disciplines

There are few outstanding issues outside of the clinical concerns. Dr. Duan (OCPB) has recommended 2 Phase 4 commitments, and Dr. Freed, pharmacology team leader, has recommended that the sponsor provide additional data about a previously known finding of mineralizations in the rat brain.

COMMENTS

The sponsor has submitted the results of five randomized controlled trials in patients with advanced PD, three of which they believe establish substantial evidence of effectiveness for istradefylline as adjunctive treatment for patients with advanced PD. In their view, these 3 studies document the effect of the drug on decreasing OFF time (as measured by the change from baseline in the percent of wake time spent in the OFF state), a commonly used outcome measure which has served as the basis for the approval of several treatments for advanced PD. There are, however, numerous findings that raise two critical questions: 1) Do the data establish that there is a clear drug-effect on decreasing OFF time, and 2) If so, do the data taken as a whole support approval. I will address each question in turn.

Do the data establish a drug effect on decreasing OFF time?

As described above, in Studies 005, 006, and 013, statistically significant between-treatment contrasts were seen for 20mg (Studies 006 and 013), 40mg (Study 005) and 60mg (Study 006) on an ANCOVA. It is worth noting that only for Studies 005 and 013 was the ANCOVA the protocol specified analysis; for Study 006, an ANOVA was pre-specified as primary. In Study 006, the contrasts on the ANOVA did not reach significance (Study 006-20mg vs pbo; p=0.09, 60mg vs pbo; p=0.08). However, Dr. Siddiqui has concluded that the ANCOVA is the more appropriate analysis for all studies, and the results on all three studies, therefore, at all doses studied, are taken as significant. Further, Dr. Bhattaram has shown that there is an exposure-response relationship for both Percent of Wake Time spent OFF and for Change from baseline in Percent Wake Time spent OFF (the primary endpoint in the clinical trials), although the slope of the latter relationship is quite shallow (see his Figure 3, page 10 of his review).

However, there are considerable data that appear to undermine the conclusion that these changes are drug-related.

Specifically, several studies have failed to establish a between-treatment difference favoring istradefylline. Study 018, an otherwise adequately designed trial that was apparently adequately powered, did not demonstrate a significant difference for either 10, 20, or 40 mg compared to placebo (indeed, the results favored placebo numerically compared to the 10 and 20mg groups). Additionally, Study 007, also an otherwise adequately designed and powered trial, failed to demonstrate an effect of 40 mg (although it did demonstrate a difference between Entacapone and placebo with a p-value of 0.06 [compared to a p-value for the istradefylline-placebo contrast of 0.73]). In addition, Study 051, a monotherapy study, failed to demonstrate an effect of 40 mg (albeit in a "different" population and on a different primary outcome measure than used in the other studies). Study 0406, although very small and clearly underpowered (N=30/group), also failed not only to show a difference favoring istradefylline, the estimate of the treatment effect numerically favored placebo over either dose of istradefylline (although the estimates were close for placebo and 40mg). In summary, two trials demonstrated the effect of a 20mg dose, but one adequately powered trial did not, and one underpowered trial showed numerical superiority of placebo compared to 20mg. One trial demonstrated the effect of a 40mg dose, but two adequately powered adjunctive trials did not (one included an Entacapone active control group, which almost reached significance, and which did reach nominal significance on a patient-rated global measure), and one adequately powered monotherapy did not; in addition, an underpowered study showed (very slight) numerical superiority of placebo compared to 40mg. Finally, only one study examined a dose of 60mg, and that study yielded a significant between-treatment contrast.

There are no obvious reasons why the negative trials should have failed (if the drug is effective), nor are there obvious reasons why the positive trials should have succeeded (if the drug is ineffective, such as breaking of the blind, etc.). The large number of trials that have failed to demonstrate an effect (especially at 40 mg, a dose that should clearly be effective if 20 and 60mgs are), is, in my experience, quite unusual for an effective treatment for PD. However, the replication of the positive results of 20mg, as well as the single positive findings at 40mg and 60mg strongly suggest to me that the drug is effective in decreasing OFF time (that is, although we have not performed the calculation, I suspect that the probability that these "4" positive findings out of the total findings [positive and negative] were positive by chance under the overall null hypothesis would be quite small). However, these results taken as a whole also very strongly suggest that the finding is relatively unstable; that is, the drug effect is quite weak.

Overwhelming supportive evidence that the effect, even if real, is extraordinarily weak, is the complete lack of any significant between-treatment findings for any secondary outcome measure at any dose. Even when drugs for PD have been approved on the basis of an effect on decreasing OFF time as the primary outcome, these drugs have always shown effects on other outcome measures

(e.g., UPDRS sub-scales, global measures). It is true that previously approved drugs have all worked (primarily, and as far as we know) by increasing dopaminergic tone, and that istradefylline (presumably) has a different mechanism of action, the effects of which might be quite different than those induced by dopaminergic agents. Indeed, it might be possible that (for reasons we do not understand), the **only** effect of istradefylline is to decrease OFF time. If this were true, we would not expect any movement on other measures of other PD symptoms (e.g., UPDRS, even in the OFF state). However, given that istradefylline is the first drug with this particular proposed mechanism for which we have received an NDA, it is impossible to know if the restricted findings seen in this application are specific to this "class", (certainly, I don't believe that the sponsor **expected** no effects on these secondary measures) or whether the lack of findings reflects the activity (or lack thereof) of a particularly non-potent member of this class of drugs. However, and critically in my view, even though we might not expect any beneficial effects on these other PD-specific tests if istradefylline only effects OFF time, we could still reasonably expect to see a benefit of the treatment reflected in measures that assess overall function or quality of life, especially in patient-rated global measures. In this regard, I note that several of the studies assessed global functioning, including patient-rated outcomes. None revealed any even nominally significant findings in favor of istradefylline. These findings, taken as a whole, lead to a consideration of the next critical question.

Do the data support approval?

As noted above, I believe the sponsor has submitted substantial evidence that istradefylline decreases OFF time in advanced PD patients (although there is little to no evidence of any increased benefit at doses greater than 20 mg). However, as I have also noted above, this finding is unstable, and therefore weak. More importantly, there is absolutely no evidence that it has any effect on other PD-associated symptoms, and, especially critically, there is no evidence that patients (or physicians) can detect any overall benefit of the treatment, as assessed by various global and "quality of life" measures. These findings raise the question of whether or not, even though there is substantial evidence of effectiveness of a decrease in OFF time (the primary outcome in the critical studies), the NDA should be approved.

Although it is true that we typically assess the approvability of a treatment based on the findings on the primary outcome measure, we must rightly ask whether or not the treatment has a place in the armamentarium. It is difficult to imagine where this treatment would fit, or, in other words, which patients should be treated with this drug. All other drugs approved for use and currently available for advanced PD patients not only decrease OFF time, but improve (relative to placebo) other PD symptoms as well. This drug is conspicuous for the absolute lack of any demonstrable effect on any other PD symptoms, despite numerous studies that were otherwise adequate and capable of demonstrating such effects.

It is essentially inconceivable that this discrepancy is an artifact of (the well-known difficulties in making) cross-study comparisons. Indeed, in the one study that included an active control (entacapone), there was absolutely no effect of istradefylline (p=0.73) and near significance for the control (p=0.06). Further, in that study, there was nominal significance in favor of entacapone on a patient-rated global measure (PGI), and no significance on this (or any other secondary measure) in favor of istradefylline. These findings, taken together, argue strongly that istradefylline is inferior in important ways to other available treatments. Although, of course, the FD&C Act does not require that new treatments be better (or even "equal") to available treatments, it is prudent to consider, as noted above, the place that this treatment would have in the armamentarium. It is difficult, in my view, to justify the approval of a treatment that is manifestly inferior to all other available treatments for this indication. PD is a serious disease, and there seems to be no justification for approving a treatment which, if used as proposed, would mean that other, more effective treatments, would be withheld (even though all of these other available treatments are symptomatic; withholding effective symptomatic treatments would not, of course, lead to permanent irretrievable disability, but effective symptomatic treatment can prevent serious consequences of PD [e.g., falls]).

It could be argued that, because istradefylline acts (presumably) via a different mechanism than all other approved PD treatments, it would be useful to have it available as adjunctive treatment. Specifically, because it makes little sense to use, as adjunctive therapy, a drug with a similar action to a patient's current treatment (for example, it might be considered inappropriate to add a dopamine agonist to a background dopamine agonist), it would appear reasonable to have available a treatment for which additive effects might be expected. This is theoretically true, but the data argue against this conclusion in this case.

Specifically, we know that dopamine agonists (e.g., pramipexole, ropinerole, rotigatine) are effective when added to Sinemet, both on decreasing OFF time and in improving other PD symptoms. We know that istradefylline is effective when added to Sinemet in decreasing OFF time, but it does not confer any other benefit. We have no data that directly speaks to how istradefylline compares to a dopamine agonist when added to Sinemet (on decreasing OFF time), but in the only study that included an active control, istradefylline was clearly inferior to that active control, a COMT inhibitor, when added to Sinemet. This finding (in concert with all of the other findings) at least raises the possibility that istradefylline is also inferior to other adjunctive treatments in decreasing OFF time, at least when these treatments are added to Sinemet.

Would istradefylline be useful specifically as adjunctive treatment when added to a dopamine agonist? Most advanced PD patients receiving a dopamine agonist are also likely receiving Sinemet. In these patients, we have evidence that istradefylline is inferior to a COMT inhibitor added to a regimen containing Sinemet and a dopamine agonist. So, it would be inappropriate to approve

istradefylline for adjunctive use to a dopamine agonist in patients who are also receiving Sinemet (because adding a COMT inhibitor in that case would presumably be superior to adding istradefylline, and not only for decreasing OFF time).

Would it be appropriate to approve istradefylline for use as adjunctive treatment to a dopamine agonist alone, without Sinemet? This is theoretically possible, but I believe the sponsor would need to supply evidence that it would be effective in this setting (recall that all of the patients in the studies presented here were also taking Sinemet), and in addition that there are advanced patients who actually are receiving treatment only with a dopamine agonist (again, if patients receiving dopamine agonists are [almost always] receiving Sinemet as well, the evidence suggests that these patients will benefit from the addition of a COMT inhibitor).

Would it be appropriate to approve istradefylline as adjunctive treatment added to an MAO inhibitor (e.g., selegeline, rasagiline)? Again, these agents are typically used in conjunction with Sinemet, and we have already seen that the addition of a COMT inhibitor in this setting appears to be superior to the addition of istradefylline. Would it then be appropriate to approve it for use in conjunction with an MAOI given alone? Again, as above with the case of dopamine agonists, the sponsor would need to demonstrate this effect, and again demonstrate that there are patients who are being treated with MAOIs who are not also receiving treatment with Sinemet.

In summary, then, although the data do not, in my view, support approval at this time, it is possible that the sponsor might be able to provide data that could ultimately justify approval, even if the only discernible effect of istradefylline is to decrease OFF time. For example, the sponsor could study patients whose other PD treatments have been explicitly optimized. If istradefylline were shown to decrease OFF time in these patients (with no effects on other PD symptoms), this would likely justify approval.

RECOMMENDATIONS

For the reasons cited above, I do not believe that this NDA should be approved at this time. I would recommend that the Agency issue a Not Approvable letter. The letter should, of course, outline the reasons that underlie our conclusion that the application cannot be approved at this time, but also suggest possible additional data that might support approval. In particular, if the sponsor could demonstrate that in patients maximally treated with available therapies the addition of istradefylline decreases OFF time, this might justify approval.

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/s/

Russell Katz
2/25/2008 01:25:58 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	022075
Submission Code	N
Letter Date	3/29/07
Stamp Date	3/29/07
PDUFA Goal Date	2/25/08
Reviewer Name	Gerald D. Podskalny
Review Completion Date	2/21/08
Established Name	istradefylline
(Proposed) Trade Name	To Be Determined
Therapeutic Class	Antiparkinsonian
Applicant	Kyowa Pharmaceutical Inc.
Priority Designation	S
Formulation	Istradefylline
Dosing Regimen	(b) (4) 20 or 40 mg/day
Indication	Adjunctive therapy in Parkinson's disease (b) (4)
Intended Population	Parkinson's disease

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Istradefylline should be "not approvable" based on the failure to demonstrate clinical efficacy at the 10 mg, 40 mg or 60 mg dose in accordance with the agency standard of having two supporting well-controlled clinical trials. Additional information is needed to establish istradefylline improves patient function or how they feel. Studies demonstrating significant improvements in global measures of improvement or severity and improvements in quality of life are important in establishing clinically meaningful improvement in patients with PD. Replication of a statistically significant outcome on the primary efficacy variable for the 40 mg dose is also important in supporting the efficacy claim. The sponsor should demonstrate that the 40 mg/day dose is superior to the 20 mg/day dose or the primary and perhaps a global or quality of life measure.

1.2 Recommendation on Post-marketing Actions

If istradefylline is ultimately approved marketing in the U.S. post-marketing data regarding the association of istradefylline with Impulse Control Disorder should be presented in the product label. Additional information concerning the association of ICDs with istradefylline should be monitored wit greater interest in the first 3 years after approval.

1.2.1 Risk Management Activity

There is no recommendation for a risk management plan.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

If istradefylline is approved the sponsor should develop a plan to monitor for Impulse Control Disorders in future trial in subjects with Parkinson's disease and Restless Legs Syndrome. The monitoring should involve active surveillance, the modified Minnesota Impulsive Disorders (mMIDI), positive responses to questions regarding ICDs trigger a structured interview (SCID). The SCID provides a framework that more uniformly assesses subjects enrolled in clinical trials who experience symptoms of ICD.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The applicant submitted safety data from 38 completed Phase 1 to 3 studies and 3 ongoing studies. The efficacy data from 9 Phase 2 and 3 studies in subjects with Parkinson's disease are presented in the submission. Four pivotal Phase 2b/3 studies 6002-US-005, 6002-US-006, 6002-US-013, 6002-US-018 and an active comparator study 6002-EU-007 are relevant to the applicant's efficacy claim. The long-term safety experience in this submission includes integrated data from one completed long-term study and 2 ongoing long-term studies.

1.3.2 Efficacy

Efficacy Claim:

Istradefylline is a selective adenosine A2A receptor antagonist the proposed indicated is for "adjunctive therapy to levodopa/carbidopa (b) (4) Parkinson's disease (b) (4)

Overall Design: Double-blind, randomized, placebo-controlled, parallel-group, and fixed-dose studies. In Study 6002-EU-007, entacapone was included as an active comparator to establish the validity of the study. Each study lasted12 weeks except study 6002-EU-007, this lasted 16 weeks.

Eligibility Criteria**:**

- Subjects must be be at least 30 years of age
- Subjects diagnosed with Parkinson's disease as determined by the United Kingdom Parkinson's Disease Society criteria
- The severity of PD subjects must have was Hoehn and Yahr stages 2 to 4.
- Subjects must be experiencing end-of-dose wearing-off in response to treatment with levodopa.
- Subjects were required to be on levodopa with carbidopa or benserazide for at least 1 year.

- They must have taken levodopa at least 4 doses/day for the Phase 2b studies and at least 3 doses/day for the Phase 3 studies.

- Their levodopa regimen must have been stable for at least 4 weeks before randomization into their respective clinical trial..

- Subjects taking a stable regimen of other adjunctive antiparkinsonian medications were allowed to continue these medications during the trials

- Awake time per day spent in the OFF state at study entry was an average of at least 2 hours in Phase 2b and at least 3 hours in Phase 3 studies.

The Primary Endpoint for all of the 5 efficacy trials was "The Change from Baseline to Endpoint in the percentage of awake time per day spent in the OFF state", based on the 24-hour ON/OFF patient diary developed by Hauser et al.

Multiple secondary endpoints assessments varied slightly between the 5 efficacy trials, they were based on the 24-hour ON/OFF Patient Diary, UPDRS, CGI, Patient Global Impression -Improvement (PGI-I) scores, Parkinson's Disease Questionnaire (PDQ), and Medical Outcomes Study 36-item Short Form (SF-36).

Results of Efficacy Trials

Summary of Clinical Trail Data for The Primary Endpoint at The 20 mg Dose

Study (N)	Support Approval Mean LMS Δ from baseline	Fail to Support Approval Mean LMS Δ from baseline	P value difference compared to placebo
KW6002-US-006 (163)	ANCOVA -7.83%	ANOVA -7.72%	ANOVA (ANCOVA) 0.088 (0.026)
KW6002-US-013 (112)	-9.49%		0.025 ANCOVA
KW6002-US-018 (144)		-6.81%	0.408 ANCOVA
6002-0406 (31)		-4.90%	0.495 ANCOVA

Summary of Clinical Trail Data for The Primary Endpoint at The 40 mg Dose

Study (N)	Support Approval Mean LMS Δ from baseline	Fail to Support Approval Mean LMS Δ from baseline	P value difference compared to placebo
KW6002-US-005 (129)	-10.81% ANOVA		0.007 ANOVA
KW6002-US-018 (145)		-8.97%	0.714 ANCOVA
KW6002-EU-007 (158)		-5.14%	0.729 ANCOVA
6002-0406 (28)		-7.72%	0.936 ANCOVA

The 10mg/day and 60 mg/day Dose of Istradefylline

(b) (4)

(b) (4) Only the 6002-US 006 study examined the 60 mg dose of istradefylline. The results at 60 mg were the same as for the 20 mg dose in that trial, with only the supporting ANCOVA analysis demonstrating superiority over placebo and the primary ANOVA analysis failing to demonstrate a benefit over placebo. The 10 mg/day dose of istradefylline failed to demonstrate superiority over placebo in both the 6002-US-018 study and in the smaller 6002-0406 study.

Efficacy Conclusion

Considering the entire body of clinical trials evidence, istradefylline does not demonstrate consistent superiority compared to placebo in subjects with advanced Parkinson's disease at 10 mg, 20 mg or 40 mg/day. Two undisputed supporting trials, one at 20 mg/day and another at 40 mg/day demonstrate statistically significant superiority of istradefylline compared to placebo based on analysis of the primary endpoint. Other clinical trials with nearly identical design, subject characteristic and the same primary endpoint fail to demonstrate efficacy of istradefylline over the entire dose range (b) (4). Istradefylline does not meet the agency standard of two well controlled clinical trials at the 40 mg dose and only meets this standard at the 20 mg/day dose if the results of the supportive ANCOVA analysis in the 6002-US-006 are accepted.

Examination of key secondary endpoints CGI, quality of life measures (PDQ-39, SF-36) and UPDRS data indicates even when statically significant effects of istradefylline is demonstrated using the primary endpoint it is not accompanied by a clinically recognizable effect in global function or quality of life. Istradefylline fails to achieve a statistically significant between group difference, in any of the key secondary outcome measures, in any of the 5 pivotal trials. The data concerning secondary endpoint do not demonstrate subjects feel or function any better on istradefylline compared to placebo.

1.3.3 Safety

Safety Summary

The sponsor's assessment of safety appears to be adequate and it was performed with reasonable diligence. There were no safety related events that were serious or life threatening. The incident of death was similar for placebo and istradefylline treated groups. The cause of death was consistent with expected causes of death for the age group recruited into the studies and disability caused by PD. Deaths that occurred in uncontrolled long-term trials were similar in rate and cause of death compared to reports in the published medical literature.

In general, TEAEs were more common in the istradefylline group compared to placebo. The percentage of serious adverse events that occurred in controlled clinical trials were similar for the placebo and treatment groups. More subjects in the istradefylline treated groups discontinued participation in their respective clinical trial compared to placebo. Dyskinesia,

Parkinson's symptoms and nausea were the most commonly given reasons for withdrawal from the trial. Analysis of TEAEs by preferred terms, higher level, higher-level group terms, system organ class and analysis of standardized MedDRA queries (SMQ) did not find a pattern of a previously not described serious or common TEAE.

The most common treatment emergent adverse events were dyskinesia, nausea and dizziness. Of these, nausea demonstrated a clear dose-response relationship up to the highest dose of 60 mg/day. Dyskinesia was greater in all of the istradefylline treated groups without a clear dose response relationship. There is a suggestion for a disease severity (measured by Hoehn & Yahr scale)-relationship with dyskinesia at the 40 mg/day dose in the pool 1 data but the number of subjects with Hoehn and Yahr stage 4 PD or greater (most severe) was small, making it difficult to interpret.

There were no significant changes in vital sign parameters by dose or duration of exposure. Study 6002-US-006 monitored for signs of orthostatic hypotension but did not find a significant difference between the placebo and istradefylline for pulse or blood pressure changes.

Clinical laboratory investigations analyzed by measures of central tendency, shift tables, outliers and individual lab parameters or index cases did not find additional evidence for organ system injury clearly associated with istradefylline.

The potential association of istradefylline with impulse control disorders is unexpected based on the drug's mechanism of action. The pivotal trials and long-term safety trials were not design to monitor for this particular TEAE.

Reviewer's Safety Conclusion

Istradefylline does not appear to be associated with sudden or idiosyncratic serious adverse events. The adverse event profile of this medication indicates adverse events can be monitored clinically or with clinical laboratory evaluations. The sponsor should consider adding a plan to evaluate the incidence and severity of impulse control disorders in future clinical trials of istradefylline.

1.3.4 Dosing Regimen and Administration

The recommended dose of istradefylline is (b) (4) 20 mg/day or 40 mg/day taken orally, with or without food. (b) (4)

1.3.5 Drug-Drug Interactions

In vitro studies indicate that istradefylline is predominantly metabolized via CYP3A4 with minor contributions from other isoenzymes such as CYP1A1/1A2, CYP2C9, CYP2C18, and CYP 2D6. Ketoconazole had no effect on istradefylline mean C_{max}, although the mean AUC

increased by 2.5-fold. The 2.5-fold increase in AUC indicates that a 20 mg dose can be safely administered with ketoconazole. (b) (4) The pharmacokinetic interaction between 40 mg/day istradefylline and 40 mg atorvastatin was evaluated in a clinical study. Multiple doses of 40 mg/day istradefylline with a single 40 mg dose of atorvastatin resulted in an increase in the atorvastatin C_{max} and AUC by 1.5-fold versus administration of atorvastatin alone. The sponsor does not provide a recommendation regarding a dose adjustment for atorvastatin when it is given with istradefylline but monitoring patients for adverse effects associated with atorvastatin is advised.

There were no clinically relevant differences in the TEAE profile of istradefylline compared to that of placebo f extrinsic factors (current smoking status and time since initiation of levodopa) and concomitant medication use (anti-hypertensive, dopamine agonists, COMT inhibitors, and combination of dopamine agonists and COMT inhibitors).

1.3.6 Special Populations

Smoking approximately 1 pack of cigarettes/day reduces the exposure (AUC 0-24) by 38% the sponsor advises that (b) (4) Smoking is less common in Parkinson's disease patients and about 5% or less of study participants were current smokers at the time they were taking istradefylline.

Hepatic impairment Child-Pugh B category, who were non-smokers had approximately a 3.3X greater exposure compared to health subjects. The T1/2 more than doubled in non-smokers with hepatic impairment. In patients with hepatic impairment the sponsor recommends a dose istradefylline dose of (b) (4) mg/day. (b) (4)

2 INTRODUCTION AND BACKGROUND

The cardinal features of Parkinson's disease (PD) are tremor at rest, bradykinesia, rigidity and postural instability. The signs and symptoms of PD ate though to result from the loss of dopamine producing neurons in the Substantia Nigra (SN). This neuronal loss is responsible for a disruption in the normal functional activity on basal ganglia circuitry leading to decrease in the excitatory output of the direct (nigrostriatal) pathway and an increase in the inhibitory output of the indirect pathway. The net effect caused by the abnormal circuitry is to inhibit input to the thalamus and cortex causing the motor symptoms of PD.

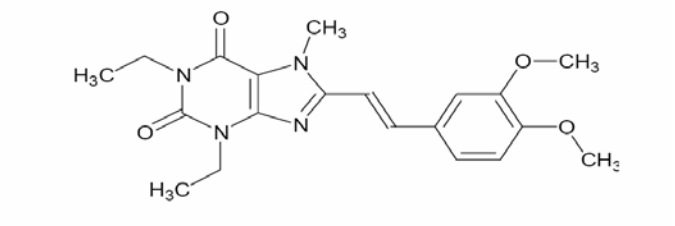
The effect of inhibiting Adenosine A2A receptors would cause a net inhibitory influence

on the indirect pathway decreasing the inhibitory influence on the thalamus and cortex attenuating the motor signs in PD. Istradefylline functions as a selective adenosine A2A receptor antagonist which in animal models of PD has been found to ameliorate the motor signs of PD.

2.1 Product Information

The established name for the product of Kyowa's NDA application is Istradefylline the sponsor has not proposed a trade name at the time of this review. The drug substance appears as light yellow-green, needle-shaped crystals.

Chemical Structure of Istradefylline



Chemical Name (IUPAC)
(E)-8-(3,4-Dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione

Molecular Formula: $C_{20}H_{24}N_4O_4$

Molecular Weight: 384.43

The investigational drug product consists of (b) (4) 20 mg and 40 mg tablets of Istradefylline Lactose, (b) (4) crospovidone, polyvinyl alcohol and (b) (4) coating. They are biconvex shaped, peach colored, film coated tablets. The shape of each biconvex tablet is determined by the tablet strength: (b) (4) the 20 mg tablets are pillow-shaped; and the 40 mg tablets are almond shaped. (b) (4) 20 or 40" on the other side, depending on the tablet strength. The product is packaged in polyethylene bottle (b) (4). The product is best stored at room temperature between 59-86 degrees Fahrenheit.

2.1.2 Chemical Class

Istradefylline is a New Molecular Entity (NME) an Adenosine A2A receptor antagonist.

2.1.3 Pharmaceutical Class

A2A receptors are expressed mainly on the axon terminals of medium spiny neurons (MSNs) in the striatum and the globus palidus externa (GPe). Their function in modulating the activity in the indirect pathway is discussed in detail in section 5. The net effect of Adenosine A2A receptor activation results in GABAergic input to the globus pallidus interna (GPi) and

eventually to the thalamus and areas motor cortex. Antagonism of Adenosine A2A receptors is expected to reduce the inhibitory out from the GPi to the thalamus and eventually to areas of cortex reducing the hypokinetic motor symptoms of PD.

2.2 Currently Available Treatment for Indications

Although the produce is the first in a new proposed class of medications there are a number of marketed products sharing the same indication as the one sought by the sponsor for istradefylline. The medications listed below are marketed products with demonstrated efficacy indicated for the symptomatic treatment of PD.

Table 2.1 Medications Marketed in The U.S. for Adjunctive Treatment of Parkinson's Disease

Medication Class	Established Name	Trade Name
Dopamine Replacement	Carbidopa/Levodopa CD/LD	Sinemet, Sinemet CR
Dopamine Agonists	Bromocriptine (ergot)	Parlodel
	Pramipexole (non-ergot)	Mirapex
	Ropinirole (non-ergot)	Requip
	Apomorphine (non-ergot) injection	Apokyn
	Rotigotine (non-ergot) transdermal	Neupro
MAO Inhibitors	Selegiline (MAO-B selective)	Deprenyl, Eldepryl
	Rasagiline	Azilect
COMT Inhibitors	Entacapone	Comtan, Stalevo (with CD/LD)
	Tolcapone	Tasmar
Antivirals	Amantadine	Symmetrel
Anticolinergics	Trihexyphenidyl	Artane
	Benztropine	Cogentin
	Procyclidine	Kemadrine
	Biperiden	Akineton

2.3 Availability of Proposed Active Ingredient in the United States

2.2 Important Issues With Pharmacologically Related Products

Non-specific adenosine receptor antagonists (caffeine) loose their motor stimulant effects with continued exposure. A2A receptor antagonists do not produce tolerance with repeated exposure[1].

2.3 Presubmission Regulatory Activity

Clinical Hold September 2003

Brain Mineralization

Mineralization of the thalamus and caudate was discovered during a 2-year carcinogenicity study in mice and rats. These changes were observed in rats at doses of istradefylline as low a 30 and 100 mg/kg/day. The sponsor presented data that brain mineralization was not observed at 3, 6 and 30 mg/kg. The mineralization particles contained calcium and phosphorus and appeared to be confined to blood vessels. The particles were occlusive in some case but collateral channels were developing. There was no evidence of tissue necrosis, hemorrhage, inflammation or glial nodules according to the sponsor. Studies in dogs at doses of 10, 30 and 100 mg/kg/day for 52 weeks did not demonstrate brain mineralization KHK/45/982101 and 983028.

The sponsor completed a calcium homeostasis in rats (R-04-171-12278), requested a peer review pathology consult and hired Consultants in Pathology and toxicology to re-evaluate the slides demonstrating mineralization in the brains of rats. Results of the special CNS stains of the tissue requested by the division were included in the re-evaluation report. The sponsor convened an expert panel of medical and regulatory specialists who concluded the finding of brain mineralization observed in mice and rats were related to aging and istradefylline had a "favorable benefit/risk profile".

The concern regarding brain mineralization prompted the division to recommend discontinuing all human trials except US-006 until the matter was studied in more detail by the sponsor. The first long-tern safety studies 6002-US-007 was stopped and after approximately 1 year off istradefylline 142 of those patients were enrolled into a new long-term safety study of istradefylline INT-001. The sponsors also closed the initial study of istradefylline for the treatment of major depression. After the results of additional studies, histopathological peer review and the opinion of the expert panel were presented to the division, clinical trials were allowed to resume. The division questioned the sponsor concerning human autopsy information but no deaths were reported on istradefylline at the time of the division's request (Type A meeting, April 14, 2004).

Waivers

A pediatric waver was granted to the sponsor on July 25, 2005. Istradefylline is indicated for adjunctive therapy in patients with advanced Parkinson's disease, therefore studies in the pediatric population are impractical and use in the pediatric population is expected to be small.

2.4 Other Relevant Background Information

EOP2 Meeting Minutes 18 July 2006

The sponsor presented data from the same 5 pivotal trials forming the basis of the efficacy evaluation in this NDA application. The data presented in advance of the meeting indicated a significant statistical difference on the pre-specified primary outcome measure , in favor of istradefylline in two trial of the 20 mg dose. The second trial supporting approval of the of the 20 mg dose did not reach statistically significant level on the pre-specified ANOVA method of analysis and a significant difference was only demonstrated using the pre-specified supporting ANCOVA analysis. At the 40 mg dose a statistically significant was demonstrated favoring istradefylline in only one study but there were no other studies replicating this clinical trial result. Studies US-018 and EU-007 failed to demonstrate that istradefylline was superior to placebo in the study population at 10 mg, 20 mg or 40 mg.

Summary of the EOP2 meeting minutes

Replication of a positive study results were lacking for the 40 mg dose based on the primary outcome measure and pre-specified primary analysis. The US-006 study would be critical to replication of a positive outcome for the 20 mg dose. The US-006 study will be judged on the basis of the pre-specified primary analysis unless there a compelling reason the method of analysis is inappropriate. The largest and longest clinical trial US-018 is negative for all tested doses (10 mg, 20 mg, and 40 mg/day).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Wendy I. Wilson, PhD completed the CMC review and concluded istradefylline is approvable from a CMC perspective. Dr. Wilson mad a number of recommendation regarding a list of deficiencies for the drug substances and the drug product. There were two specific concerns listed below, regarding the drug product that may impact the clinical use of istradefylline directly. The reader is referred to Dr. Wilson's review for the details of the CMC review.

1. Your proposed drug product expiry of (b) (4) months is not justified based on only 12 months of long-term primary stability data. Refer to the guidance document ICH Q1E – Evaluation of Stability Data and provide justification to support your proposed expiry. Include statistical analysis of the stability data to support your proposed expiry, if appropriate.
2. Provide revised drug product labels, adding "Tablets" after the established name to indicate the dosage form. (b) (4)

3.2 Animal Pharmacology/Toxicology

The issue of greatest concern during clinical development was the potential for calcifications similar to those observed in the 2-year rat carcinogenicity study. The calcification was in the blood vessel walls and concern was raised about the potential for vascular occlusive disease. Occlusion of the vessel lumen was not seen in subsequent animal studies and the calcifications appeared to be specific to rats. Cerebrovascular accident was reported in one subject assigned to the placebo with no cerebrovascular AEs reported in the istradefylline treated groups. In addition neuropsychological testing was performed as part of the 6002-US-051 study at selected sites. This was a phase 2 study of subjects with early PD, treated with 40 mg/ of istradefylline per day (N=94) or placebo (N=82) for 12 weeks. The results did not indicate a decline in scores for the neuropsychological battery. Although the 051 study only lasted 12 weeks the were no significant differences in cognitive function in subjects who received istradefylline compared to placebo.

The Pharmacology-Toxicology review team reported no outstanding issues at this time.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor identified five clinical trials as pivotal trials, they include two phase 2b and three phase 3 clinical trials. All of the trials used the same primary endpoint, the change from baseline to endpoint in the subject's percentage of their daily awake time spent in the OFF state. The sponsor used the Parkinson's disease patient diary (Hauser version) to collect the primary endpoint data. A table listing the features of the 5 pivotal trials appears below.

4.2 Tables of Clinical Studies

Table 2.2-Pivotal Trial Results Submitted For Efficacy Review

Study I.D.	Study design	Entry Characteristics	Dose(s)	Duration	Primary endpoint(s)
6002-US-005 25 centers (22 US; 3 Canada) 23 April 2002 to 05 May 2003	Phase 2b, Randomized, Double-blind, Placebo controlled, parallel groups Randomized, n=196	Subjects ≥30 years-old, PD for >1 year, on levodopa >1 year requiring ≥4 doses/day, with motor fluctuations and end of dose wearing off totaling at least 2 hours/24 hours.	Istradefylline 40 mg Placebo	12 weeks	Change from baseline to endpoint in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary
6002-US-006	Phase 2b, Randomized,	Subjects ≥30 years-old, PD for >1 year, on levodopa >1	Istradefylline 20 mg/day	12 weeks	Change from baseline to endpoint

40 centers (38 US; 2 Canada) 23 April 2002 to 06 October 2003	Double-blind, Placebo controlled, parallel groups Randomized, n=395	year requiring ≥4 doses/day, with motor fluctuations and end of dose wearing off totaling at least 2 hours/24 hours.	60 mg/day Placebo		in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary
6002-US-013 26 centers (US) 14 July 2004 to 21 November 2005	Phase 3 Randomized, Double-blind, Placebo controlled, parallel groups Randomized, n=231	Subjects ≥30 years-old, PD for >1 year, on levodopa >1 year requiring ≥3 doses/day, with motor fluctuations and end of dose wearing off totaling at least 3 hours/24 hours.	Istradefylline 20 mg/day Placebo	12 weeks	Change from baseline to endpoint in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary
6002-US-018 74 centers (59 US, 15 Canada) 23 July 2004 to 16 November 2005	Phase 3 Randomized, Double-blind, Placebo controlled, parallel groups Randomized, n=610	Subjects ≥30 years-old, PD for >1 year, on levodopa >1 year requiring ≥3 doses/day, with motor fluctuations and end of dose wearing off totaling at least 3 hours/24 hours.	Istradefylline 10 mg/day or 20 mg/day or 40 mg/day Placebo	12 weeks	Change from baseline to endpoint in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary
6002-EU-007 56 centers 11 Nov 2004 to 03 Oct 2005	Phase 3 Randomized, Double-blind, Placebo controlled, parallel groups	Subjects ≥30 years-old, PD for >1 year, on levodopa >1 year requiring ≥3 doses/day, with motor fluctuations and end of dose wearing off totaling at least 3 hours/24 hours.	Istradefylline 40 mg/day Entacapone 200 mg with every LD dose Placebo once daily	16 weeks	Change from baseline to endpoint in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary

4.3 Review Strategy

The sponsor submitted the NDA application using the eCTD format. The submission would be accessed through GlobalSubmit Reviewer through the Electronic Document Room (EDR). On May 15, 2007 the member of the review attended a training session at the sponsor's request concerning the use of Global Submit and the ECTD format. The training session was specific to the sponsor's NDA application, which was used during the demonstration. Besides

the review team members, representative from Kyowa and the Office of Business Process Support attended the meeting. At the conclusion of the filing meeting held on June 12, 2007 the NDA application could be filed with specific requests made by the sponsor and specific review divisions.

Efficacy Review

Studies 6002-US-005, 006, 013, 018 are placebo controlled trails considered for efficacy review. These studies share the same primary endpoint and use most of the same key secondary endpoints. The 6002-EU-007 study is a comparator study, istradefylline was compared to placebo and the marketed product entacapone administered as a separate tablet with carbidopa/levodopa was also compared to placebo. The 6002-EU-007 used the same primary endpoint as the other four pivotal trials but they did not use the same secondary endpoints. The trials were reviewed individually for efficacy, because the studies were so similar in design the US-005 study was described in detail as a prototypical study. The description of the remaining studies is in regards to the efficacy outcome and only highlighting the minor changes in study design or safety issues unique to the study.

Safety Review

Safety data was grouped into data pools described in detail in the integrated review of safety (ISE) in this review. Pools I (phase II/III clinical trials for the proposed indication PD), pool II (long-term safety studies) and V (controlled clinical trials for any indication, included pools I, III, IV, VI) contain the majority of the safety data. The applicant in the 4-month safety update (August 7, 2007 amendment) added pool VI to the integrated review of safety (ISS). Pool VI contained safety data from the US-051 study of istradefylline as monotherapy in early PD and the US-201 study for the treatment of Restless Legs Syndrome (RLS).

Individual Study Review

There were specific safety related issues studied in individual trials designed to address a particular concern. The 6002-US-006 study included monitoring for orthostatic hypotension in PD subjects with PD and this safety review of orthostatic hypotension in the ISS relies upon data from this study to examine the incidence of orthostatic hypotension in subjects treated with istradefylline compared to placebo. The long-term extension, open label study of the 6002-US-006 study, the US-007 study continued to look at orthostatic changes in blood pressure and pulse but without the ability to compare to a placebo group.

4.4 Data Quality and Integrity

Site 019 in the sponsor's study KW-6002-US-005 and site 074 in study KW-6002-US-006 were selected for DSI inspection because they enrolled the highest number of subjects into their respective trials

The sponsor submitted an amendment (sequence # 0007) dated August 22, 2007 to informed the agency of a data sorting error affecting the PDDIARY1 derived datasets in studies 6002-US-005, 006, 007. The sponsor described the error as data sorting error causing a mistake labeling of the AM/PM designation for the time of day for affected PD diary entries. The sponsor indicated the error did not effect calculation of the primary endpoint for the other derived (analysis) datasets PDDIARY 2 and 3. The percent of the awake part of the day each subject spent in the OFF state was not affected by the sorting error. After a teleconference with the sponsor, it seems the data-sorting problem was discovered around the same time the DSI inspection of site 019 occurred.

Site 019 was selected for DSI inspection because was the highest enrolling site in the US-005 study. The DSI inspector found the same discrepancy in the AM/PM designation between the data recorded on the CRF and in the sponsor's electronic dataset (XPT file). Additional data discrepancies discovered included duplicate entries for the subject's clinical state for a single diary time period where only one entry per 30 minute time period is valid and missing diary entries. For example, subject 6002-US-(b) (6) during visit week 2 at 1:30 AM-2:00AM and 2:00 AM to 2:30 AM time slots indicates the subject was both "asleep" and "on with dyskinesia". There are 5 possible choices to describe the subjects clinical PD state for each 30 minute time diary time block, but the subject can only choose state for each one 30 minute PD diary time interval. The entry of 2 clinical state for the same 30 minute block of time invalidates the diary entry. There are instances where the combination of duplicate entries and missing time slots exceeds 2 hours in a single 24-hour diary, which invalidates the entire 24-hour diary under the sponsors rules of diary validation. The sponsor's electronic raw datasets tabulating the subject's diary entries in the US-005, this clinical reviewer visually scanned 006 and 013 studies and numerous duplicate entries were detected. The pre-specified rules for data handling described n the study protocol allow for duplicate entries. The sponsor created a hierarchy of all or the possible responses and ranked them from worst to best. Duplicate (invalid) entries on the subjects PD diary were considered missing in the ITT analysis. For the worst case analysis duplicate entries were transformed to a single entry according to the hierarchy and that value was imputed into the sponsor's database. In addition, a selected review of PD diary entries from subjects who died during the trial uncovered a diary data points for time were marked on the CRF but missing from the sponsor's electronic dataset.

Typically clinical trial data is enter using double data entry techniques which should detect and duplicate data entries for a variable where there can only be one response. This raises the suspicion that adequate safeguards against faulty data entry were not in place. The division made a formal request sent to the sponsor by email requesting CRF copies of selected PD diaries on October 17, 2007, the sponsor did not comply with the request until December 20, 2007. Copies of the Parkinson's disease diaries from the CRF were to compare the CRF to the sponsor's electronic dataset. The purpose of the request was to investigate the integrity of the data entry for the primary efficacy variable from the CRF to the sponsor's electronic database. An additional goal was confirm that data validation rules for the PD diaries were followed according to the pre-specified data analysis plan.

4.5 Finding of The DSI Inspection

Table 2.3-From DSI inspection Report

II. RESULTS (by site):

Clinical Investigator/Site	Protocol(s)	Inspection Date	EIR Received Date	Final Classification
Dr. Lynne Struck, Site #19 Iowa Health Physicians 1221 Pleasant Street, Suite 300 Des Moines, IA 50309	6002-US-005	7/30/07- 8/1/07	8/27/07	NAI
Dr. Dee Silver, Site #74 Coastal Neurological Medical Group, Inc. 9850 Genesee Avenue, Suite 740 La Jolla, CA 92037	6002-US-006	8/27/07- 9/4/07	9/19/07	VAI

Key to Classifications
NAI - No deviation from regulations. Data acceptable.
VAI - No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI - Response Requested = Deviation(s) from regulations.
OAI - Significant deviations from regulations. Data unreliable.

6002-US-005-Site #19

"The data audit encompassed a review of original source documents and sponsor-provided electronic data listings. For four subjects ((b) (6)), the audit revealed instances of discrepancies between the primary efficacy variable data contained in the original subject diaries (original source documents) and the data provided by the sponsor in the electronic data listings. Specifically, where discrepancies were found, the subjects' "on" or "off" status (primary efficacy variable) recorded in the original subject diaries was not correctly represented in the sponsor-provided electronic data listings. All of the discrepancies involved subjects who received the test article. These discrepancies were not found to be site-specific deficiencies as no data entry was done at the study site. The original subject diaries were sent from Dr. Struck's site directly to the sponsor. '

6002-US-006- Site #74

"In general, the study appears to have been conducted in compliance with protocol specified
requirements, with the exception of three subjects who did not meet protocol inclusion/exclusion criteria. Subjects (b) (6) and (b) (6) had documented histories of carcinoma within five years of study enrollment, but were not excluded from study participation in violation of the protocol. Subject (b) (6) was not on a stable regimen of levodopa/carbidopa for at least four weeks prior to randomization, in violation of the protocol inclusion criteria. Overall, however, data in sponsor-provided data listings were supported by data in source documents and case report forms, and no deficiencies related to data validation were cited."

The sponsor complied with a request from the division for copies of the subject PD diaries for a fewer number of subjects which included all of the subject diaries for site 019 in

KW6002-US005 study. The CRFs the sponsor's tabulation data sets and analysis datasets were compared to the entries o the diary portion of the CRF. The AM/PM data sorting described by the sponsor were readily apparent they were consistent with the sponsor's explanation of the effect of the error and that the integrity of the primary endpoint analysis was not affected. Duplicate and missing diary entries were few and the sponsor's validation scheme and data handling rule were follow according to the pre-specified plan. The conclusion was that the sponsor AM/PM time designation error in the tabulation datasets were consistent with the sorting error described by the sponsor. The error in the AM/PM time of day designation did not affect the integrity of the primary or secondary outcome variables. The duplicate entries were handled in accordance with the pre-specified rules for data handling described in the sponsor's study protocol. Duplicate data entries on the CFR could have been queried by the site investigator to the subject, during the visit, which would have produce a more reliable method of data correction.

4.6 Compliance with Good Clinical Practices

The sponsor attested to conducting each of the clinical trials submitted for review in compliance with 21 CFR 50 parts 56 and 312 21, CFR 50.25 and ICH E6. The sponsor also attested to conducting each of the clinical trials in accordance with national and international ethical principles for protection of human subjects in clinical research trials. The reviewer did not find evidence of unethical conduct on the part of the sponsor or the study site personnel.

4.7 Financial Disclosures

The sponsor was unable to obtain financial disclosures from 9 site investigators representing 7 study sites across all of clinical trials relating to Parkinson's disease. For the 5 phase 2b and phase 3 trials considered in this review there no site investigators listed as not providing a financial disclosure form.

5 CLINICAL PHARMACOLOGY

The symptoms of Parkinson's Disease (PD) are thought to arise form the loss of dopamine containing neurons in the substantia nigra. The resultant alteration of basal ganglia circuitry both in the direct and indirect pathways gives rise to the symptoms of PD. Adenosine A2A receptor activation increases the excitability of the indirect (striatopallidal) pathway via adenosine A2A receptors on the striatum (Putamen primarily) and globus pallidus externa (GPe). A2A receptors are expressed mainly on the axon terminals of medium spiny neurons (MSNs) which also have Dopamine D_2 receptors. The MSNs contain GABA and enkephalin, A2A receptor activation in the striatum increases excitability of the MSNs in these 2 brain areas by presynaptically reducing intrastriatal GABAergic inhibition onto MSNs. In the GPe, A2A receptor activation enhances GABA release from the axon terminal of MSNs. In the striatum and GPe increase the excitability of GABAergic striatopallidal pathway, which suppresses

excitability of globus pallidus interna (GPi) neurons that project to the STN then to the ventralis anterior (VApc) and ventralis lateralis pars oralis (VLo) nuclei of the thalamus. This in turn projects to the motor, pre-motor and supplementary motor areas of cortex resulting in the hypokinetic symptoms of PD. Antagonism at the Adensoine A2A receptor causing a reduction in the inhibitory GABAergic (See figure) tone on the thalamus and eventually reducing inhibitory tone on the cortex attenuating the symptoms of PD.

Figure 5.1
Modified from
Mahlon R. DeLong, MD; Thomas Wichmann, MD. Arch Neurol. 2007;64:20-24 [2]

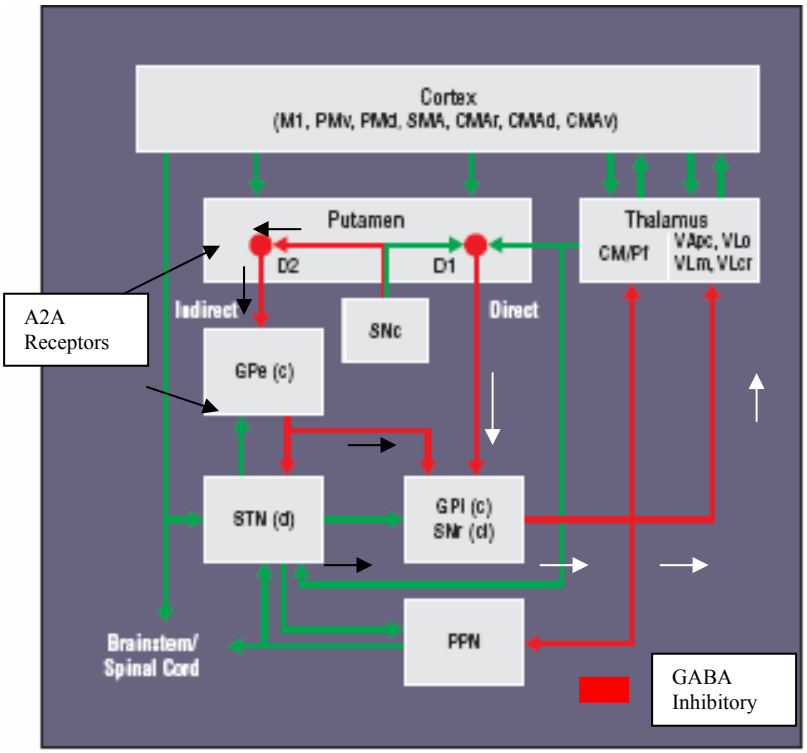


Figure. Intrinsic circuit anatomy of the motor circuit. The cortical motor areas give rise to a specific motor subcircuit. Red arrows indicate inhibitory (γ-aminobutyric acid [GABA]–ergic) connections; green arrows, excitatory (glutamatergic) connections. CM indicates centromedian nucleus of thalamus; CMAr, rostral portion of cingulate motor area; CMAd, dorsal portion of cingulate motor area; CMAv, ventral portion of cingulate motor area; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; M1, primary motor cortex; Pf, parafascicular nucleus of the thalamus; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VApc, ventral anterior nucleus of thalamus pars parvocellularis; VLm, ventrolateral nucleus of thalamus pars medialis; VLo, ventrolateral nucleus of thalamus pars oralis; VLcr, ventrolateral nucleus of thalamus rostral pars caudalis; c, caudal; cl, caudolateral; and d, dorsal.

5.1 Pharmacokinetics

Table 5.1-Pharmacokinetic Parameters of Istradefylline after Single-Dose Administration of the Istradefylline 40-mg Intended Commercial Tablet in Cohort 2 (Study 6002-US-022) (Kyowa Table)

Parameter	Mean (SD)
N	65
C_{max} (ng/mL)	178.5 (52.1)
T_{max} (h) [a]	3.00 (1.00 to 8.00)
AUC_{0-t} (ng·h/mL)	7707 (3570)
$AUC_{0-\infty}$ (ng·h/mL)	8223 (4007)
$t_{1/2}$ (h)	69.1 (30.6)

[a] Values reported are median (range).
Note: N = maximum number of subjects with data.
Source: Clinical Study Report 6002-US-022, Table 11.4.2-3

5.1.1 Food Effects

Food shortens the Tmax and increases in the Cmax fed state from 168 ng/mL to 271 ng/mL. The t ½ and AUC also increase slightly when istradefylline is administered with food.

Table 5.2-Arithmetic Mean Pharmacokinetic Parameters for Istradefylline in Fed and Fasted States (Kyowa Table)

	Fed		Fasted	
PK Parameter	N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
$AUC_{0-\infty}$[a] (ng·h/mL)	24	8923.17 (4775.16)	24	7203.64 (3630.52)
AUC_{0-t}[a] (ng·h/mL)	25	8179.51 (4314.72)	25	6629.53 (3562.50)
C_{max}[a] (ng/mL)	25	271.28 (64.97)	25	168.14 (46.02)
$t_{1/2}$[a] (hour)	24	79.82 (41.20)	24	69.99 (33.36)
K_{el}[a] (l/h)	24	0.0121 (0.0079)	24	0.0132 (0.0079)
T_{max}[a] (hour)[b]	25	2.00 (1.00 - 3.00)	25	3.00 (1.00 - 8.00)
Vz/F[a] (L)	24	589.82 (361.12)	24	669.29 (385.72)
$AUC_{0-\infty}$[c] (ng·hr/mL)	23	9135.70 (4765.01)	23	7247.76 (3705.53)
$t_{1/2}$[c] (h)	23	82.01 (40.67)	23	72.15 (32.36)
Vz/F[c] (L)	23	597.23 (367.36)	23	690.13 (380.32)

[a] Parameter is summarized for subjects who completed the study under both fed and fasted conditions.
[b] The T_{max} is presented as median (min, max).
[c] Subjects who completed the study under fed and fasted conditions and had estimable K_{el} values in both conditions.
Source: Tables C-1 and C-2, Pharmacokinetic Report

5.1.2 Effect of Smoking

Smoking approximately 1 pack of cigarettes/day reduces the exposure (AUC 0-24) by 38% (b) (4) . Smoking is less common in Parkinson's disease patients and about 5% or less of study participants were current smokers at the time they were taking istradefylline.

5.1.3 Hepatic Impairment

Hepatic impairment Child-Pugh B category, who were non-smokers had approximately a 3.3 X greater exposure compared to health subjects. The T1/2 more than doubled in non-smokers with hepatic impairment. (b) (4) Subjects who are smokers with hepatic impairment based on a comparison of the AUC 0-24 which is 58% of health non-smokers. (b) (4)

Table 5.3-Pharmacokinetic Parameters for Subjects with Hepatic Impairment Compared to Healthy Non-Smokers(Study 6002-US-016) (Kyowa Table)

Parameter	Mean			
	Healthy Non-smokers	Healthy Smokers	Hepatic Impairment Non-smokers	Hepatic Impairment Smokers
N	7	7	7	7
f_{ss} (ng/mL)[a]	0.86	0.97	0.62	0.90
AUC_{0-24} (ng·h/mL), steady state	8913.9	5205.64	30192 [b]	5183.5
$t_{1/2}$ (h)	117.99	55.55	287.61	99.63

[a] Fraction of steady-state achieved on Day 14.
[b] Predicted AUC value at steady-state.
Note: N = maximum number of subjects with data.
Source: M 2.7.2.3.7.5, Table 2.7.2-62

5.2 Pharmacodynamics

5.3 Exposure-Response Relationships

Pharmacometrics Review

Joo Yeon Lee, Ph.D conducted the primary pharmacometrics review, the conclusion reached by the pharmacometrics review team follows in the paragraph below. The reader is referred to the pharmacometrics review for more detailed information.

Based on the pharmacometrics analysis, the following are the recommendations

1. The relationship between exposure (AUC) of Istradefylline and % OFF Time is shallow. A six fold increase in AUC does not result is a corresponding increase in the % OFF Time.

2. The exposure in smokers is 38% lower than non-smokers. The label should state the differences in AUC in smokers and non-smokers and allow for increment in dose in smokers as needed.

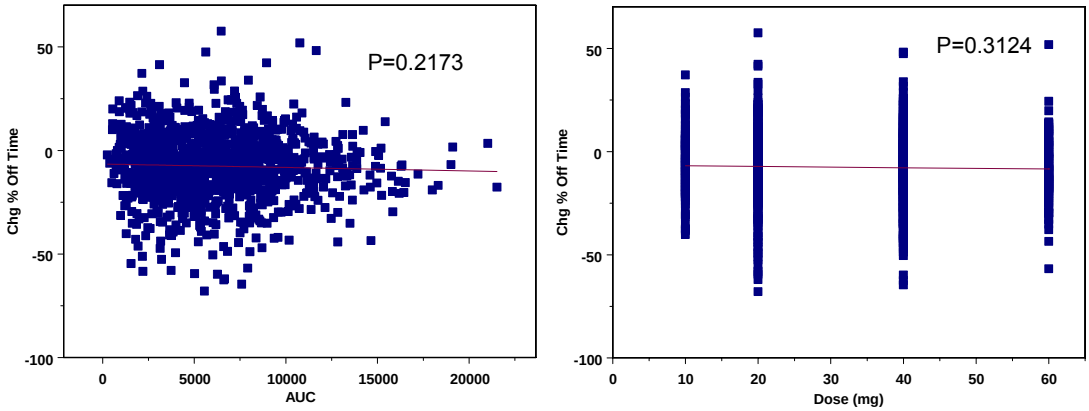
Clinical Pharmacology Review

Dr. John Duan, Ph.D was the primary Clinical Pharmacology reviewer for this NDA application. This excerpt from his review described his analysis of the exposure response relationship for istradefylline.

The figure below shows the relationship between dose and the observed effects (least square mean change from baseline at the end of the study) versus dose in the three positive clinical trials.

1. Through our analyses described in section 2.2.4.1, the difference of effectiveness among different dose levels is not significant. The dose response has not been shown, this is in contrast to the applicant's more complex approach.

    - As shown in the following figures, the exposure (either using AUC or dose) and response (clinical endpoint: change of percent OFF time from baseline at the end of the studies) do not have significant relationship.



- Either univariate or multivariate analyses, or pair wise comparisons, there is no significant difference of the primary clinical endpoint (change of percent of OFF time from baseline at the end of the studies) among different dose groups as shown in the following table. Predictors used in the following table include dose, STDY (study), BOFF (baseline off time), DOPA (concomitant dopamine agonist), COMT (catechol O-methyltransferase inhibitor), SELG (concomitant selegiline), AMAT (concomitant amantadine), age, LYRS (years of start of levodopa therapy), TPD (diagnosis of Parkinson's Disease year), TOMC (time since onset of motor complications). Only baseline off time, age, and LYRS are significant predictors.

Reviewer Comment

I agree with the Clinical Pharmacology and the Pharmacometrics reviews that the effect of istradefylline on the primary outcome variable examined by dose or exposure are small. The small clinical effect is illustrated in the results of the 6002-US 018 study, which is the largest of the pivotal trials and it is the only trial to study all of the doses included in sponsor's application. The 018 study finds only a small change in the from baseline to endpoint in effects of istradefylline at 10 mg/day, 20mg/day and 40 mg/day on the primary outcome variable. The maximum difference in the percent of daily awake time spent in the OFF state is -3.41% (difference between the 10mg/day and 40 mg/day doses) and the difference between the 10 mg and 20 mg per day dose is only 0.44%. Analysis of key secondary endpoints such as the PGI-I, PDQ-39 and UPDRS subscales fails to find a significant difference in effect between the doses of istradefylline, indicating subjects did not realize an improvement in their function. The results of the PDQ-39 indicated subjects did not feel their quality of life improved on istradefylline compared to placebo. The failure to improve the UPDRS score, global measures of improvement (CGI-I, PGI-I) and quality of life measures is a consistent result found in the sponsor's pivotal trials.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

INDICATIONS AND USAGE

The indication proposed by Kyowa as stated in M1, 1.14.1.3 of the sponsor's application is as follows.

Istradefylline is a selective adenosine A2A receptor antagonist the proposed indicated is for "adjunctive therapy to levodopa/carbidopa (b) (4) Parkinson's disease (b) (4)".

Reviewer Comment

The proposed indication for istradefylline is limited to adjunctive therapy in patients with advanced PD. (b) (4) The exploratory study, KW6002-EU-04 examined the potential use of istradefylline in a group of 24 patients with early PD. The small size of the trial did not allow for definitive conclusions but the results did not indicate improvement compared to placebo, even with subgroup analysis of a group of patients with more severe UPDRS part III scores.

As PD advances the two major motor complications patients experience are "wearing-off" and dyskinesia. Many of the available treatment strategies to treat patients with motor complications in advanced PD patients improve wearing off at the expense of worsening dyskinesia. The clinical rational for developing istradefylline for patients with advanced PD is the sponsors belief it would reduce the amount of "OFF" time advanced PD patients experience each day without increasing dyskinesia.

6.1.1 Methods

The efficacy review encompassed five placebo controlled, double-blind trials, comparing groups that received single doses of istradefylline. All five studies had a similar design and shared the same primary outcome variable. The secondary outcome variables were similar for the most part but there were variations in the use of global measures and quality of life measures.

The sponsor did not include the data sets from study 6002-0406 performed in 13 centers in Japan, randomized 89 subjects in the application, a study summary was included in the submission. Safety and efficacy data from 6002-0406 is included in the application. A summary of the efficacy results of the 6002-US-051 study of istradefylline as monotherapy in subjects with stage 1-2.5 (Hoehn & Yahr) PD is also presented in this review.

Table 6.1-Pivotal Trial Results Included in the Efficacy Review

Study I.D.	Study design	Entry Characteristics	Dose(s)	Duration	Primary endpoint(s)
6002-US-005 25 centers (22 US; 3 Canada) 23 April 2002 to 05 May 2003	Phase 2b, Randomized, Double-blind, Placebo controlled, parallel groups Randomized, n=196	Subjects ≥30 years-old, PD for >1 year, on levodopa >1 year requiring ≥4 doses/day, with motor fluctuations and end of dose wearing off totaling at least 2 hours/24 hours.	Istradefylline 40 mg Placebo	12 weeks	Change from baseline to endpoint in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary
6002-US-006 40 centers (38 US; 2 Canada) 23 April 2002 to 06 October 2003	Phase 2b, Randomized, Double-blind, Placebo controlled, parallel groups Randomized, n=395	Subjects ≥30 years-old, PD for >1 year, on levodopa >1 year requiring ≥4 doses/day, with motor fluctuations and end of dose wearing off totaling at least 2 hours/24 hours.	Istradefylline 20 mg/day 60 mg/day Placebo	12 weeks	Change from baseline to endpoint in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary
6002-US-013 26 centers (US) 14 July 2004 to 21 November 2005	Phase 3 Randomized, Double-blind, Placebo controlled, parallel groups Randomized, n=231	Subjects ≥30 years-old, PD for >1 year, on levodopa >1 year requiring ≥3 doses/day, with motor fluctuations and end of dose wearing off totaling at least 3 hours/24 hours.	Istradefylline 20 mg/day Placebo	12 weeks	Change from baseline to endpoint in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary
6002-US-018 74 centers (59 US, 15 Canada) 23 July 2004 to 16 November 2005	Phase 3 Randomized, Double-blind, Placebo controlled, parallel groups Randomized, n=610	Subjects ≥30 years-old, PD for >1 year, on levodopa >1 year requiring ≥3 doses/day, with motor fluctuations and end of dose wearing off totaling at least 3 hours/24 hours.	Istradefylline 10 mg/day or 20 mg/day or 40 mg/day Placebo	12 weeks	Change from baseline to endpoint in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary
6002-EU-007 56 centers 11 Nov 2004 to 03 Oct 2005	Phase 3 Randomized, Double-blind, Placebo controlled, parallel groups	Subjects ≥30 years-old, PD for >1 year, on levodopa >1 year requiring ≥3 doses/day, with motor fluctuations and end of dose wearing off totaling at least 3 hours/24 hours.	Istradefylline 40 mg/day (n=159) Entacapone 200 mg with every LD dose (n=153 Placebo once daily (n-152)	16 weeks	Change from baseline to endpoint in the % of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary

6.1.2 General Discussion of Endpoints

6.1.3 Data Collection

The applicant chose the Hauser version of the Parkinson's disease diary as the instrument data collection instrument used to calculate the primary efficacy endpoint. The primary endpoint is the "Change from baseline to endpoint in the percent of "OFF" time experienced during the awake part of the day, recorded in a 24 hour PD diary. The agency approved product entacapone (Comtan™) used a similar primary endpoint, change in the proportion (expressed as a percentage) of daily "ON" time recorded in the PD Diary, in the North American Trial. Change in the percent of awake "OFF" time was a secondary outcome variable in the North American trial.

The sponsor protocol design for all of the pivotal trials included in this submission required patients to record the diary information directly on the CRF for the three days prior to the scheduled study visit. Site investigators would validate the completed diaries and ideally submit two valid diaries for each visit to the sponsor. If only one of the three diaries was valid then it would be used to calculate the primary endpoint variable. If more than 2 hours in single any 24-hour diary contained missing or invalid entries then the entire diary was invalid. The sponsor received the diary information on the CRFs and calculated the primary efficacy variable. Two complete and valid diaries were averaged with respect to the percent of awake time spent in the OFF state and used to calculate the percent of awake OFF time for each visit. If all three diaries were complete and valid, the two diaries representing the 48-hour period before the scheduled study visit were used to calculate the primary efficacy variable. The endpoint was the same for all five trial included in the submission. The PD diary has as a major shortcoming the possibility that subjects may not complete them on the specified day and time. This practice may lessen the quality of the diary data caused by inaccurate subject recall and invalid diary entries.

Changes In The Amount of Awake Time

The sponsor chose the change in the percent of the awake part of the day subjects spent in the OFF state as the primary endpoint. The conversion of the time spent in the OFF state to a percent can also present difficulties in interpreting improvement and may potentially lead to over estimation of istradefylline's treatment effect. A simply changing the amount of awake time per day may, influence the primary outcome variable without changing the amount of OFF hours. For example, if two subjects receiving istradefylline both experience two hours off time per day and they are both awake for 8 hours/day. Subject 1 receives istradefylline and in now awake for 10 hours but still has 2 hours of off time per day. Subject 2 receives placebo and they are unchanged with respect to awake hours or OFF hours. The subject in the placebo group is off 25% of their awake day, but the subject who received istradefylline improved form being off 25% of their awake day to now being off only 20% of their awake day by virtue of being awake for 2 more hours on istradefylline.

Analysis of the 6002-US-005 and 006 analysis datasets for change in total asleep hours by treatment and by visit did not find a difference of more that 0.5 hours between any of the treatment groups or study visits making it unlikely a change in awake (or asleep) hours was responsible for between group differences in the primary endpoint. The mean difference in total asleep time between groups and between treatment groups by visit was on average 0.5 hours or less. The were no major differences in the amount of time spent asleep that could account for an improvement in the istradefylline treated groups.

6.1.4 Secondary Endpoints

1. Secondary endpoints (Similar in all studies except EU-007)

PD Diary Data

Off Time

1. Percent of waking time spent in OFF state at weeks 2, 4, 8, 12

2. Total hours spent in OFF state for weeks 2, 4, 8, 12.

On Time

On With No Dyskinesia

1. Percent of awake time spent in the ON state without dyskinesia at weeks 2, 4, 8, 12 and endpoint

2. Total hours awake time spent in the ON state without dyskinesia at weeks 2, 4, 8, 12, and endpoint

On With Dyskinesia

1. Percent of awake time spent in the ON state with dyskinesia (non-troublesome and troublesome) weeks 2, 4, 8, 12 and endpoint

2. Total hours awake time spent in the ON state with dyskinesia (non-troublesome and troublesome) at weeks 2, 4, 8, 12 and endpoint.

***On with Non-troublesome Dyskinesia**

1. *Percent of awake time spent in the ON state with non-troublesome dyskinesia at weeks 2, 4, 8, 12 and endpoint.

2. *Total hours of awake time spent in the ON state with non-troublesome

dyskinesia at weeks 2, 4, 8, 12 and endpoint.

Non-troublesome Dyskinesia-is defined by the sponsor as dyskinesia that did not interfere function or cause meaningful discomfort

On with Troublesome Dyskinesia

1. Percent of awake day spent in the ON state with troublesome dyskinesia at weeks 2, 4, 8, 12 and endpoint.

2. *Total hours awake day spent in the ON state with troublesome dyskinesia at weeks 2, 4, 8, 12 and endpoint.

(*) The analysis of the secondary outcome parameters were performed ***Post-Hoc,*** **after unblinding of the treatment codes in the KW6002-US-005 trial.**
UPDRS scores during ON/OFF states:

1. UPDRS I to IV total score (including ON time rating for UPDRS subscale II and UPDRS subscale III), defined as the sum of subscales I, II, III, and IV at Weeks 2, 4, 8, 12, and endpoint.

2. UPDRS subscale II (activities of daily living) total score in an ON State at Weeks 2, 4, 8, 12, and endpoint.

3. UPDRS subscale III (motor examination) total score in an ON State at Weeks 2, 4, 8, 12, and endpoint

4. UPDRS subscale III (motor examination) total score in an OFF State at Weeks 4, 12, and Endpoint.

CGI-I and CGI -S

Clinical Global Impression - Improvement (CGI-I) and Clinical Global-Severity (CGI-S) at Weeks 2, 4, 8, 12 and at endpoint.

6.1.5 Study Design

The design of studies 6002-US-006, 007, 013, and 018 were double blind, placebo controlled comparing istradefylline in different fixed doses to placebo in Parkinson's patients with motor fluctuations. Study 6002-EU-007 was an active comparator study of istradefylline 40 mg daily to placebo and entacapone 200 mg with carbidopa/levodopa was also compared to placebo.

Summary Phase 2b/3 Pivotal Trial Designs

- **Overall Design:** Double-blind, randomized, placebo-controlled, parallel-group, and fixed-dose studies. In Study 6002-EU-007, entacapone was included as an active comparator study.

- **Study Duration:** 12 weeks (exception: Study 6002-EU-007 for 16 weeks).

- **Disease Type and Stage:** Subjects were diagnosed with Parkinson's disease as determined by the United Kingdom Parkinson's Disease Society criteria; the severity of Parkinson's disease was Stages 2 to 4 as measured by the Modified Hoehn and Yahr scale; and subjects were treated with levodopa and had end-of-dose wearing-off.

- **Levodopa Regimen:** Subjects were equired to be on levodopa and a peripheral dopa-decarboxylase inhibitor (carbidopa or benserazide) for at least 1 year. Subjects were to be on a stable regimen of levodopa (at least 4 doses/day in the Phase 2b studies and at least 3 doses/day in the Phase 3 studies) for at least 4 weeks before randomization into double-blind treatment. Other antiparkinson's medications were allowed.

- **Eligibility Criteria:** Subjects were required to be at least 30 years of age, and awake time per day spent in the OFF state at study entry was an average of at least 2 hours in Phase 2b and at least 3 hours in Phase 3 studies.

- **Primary Endpoint:** The change from Baseline to Endpoint in the percentage of awake time per day spent in the OFF state based on the 24-hour ON/OFF patient diary developed by Hauser et al.

- **Secondary Endpoints:** Additional assessments were based on the 24-hour ON/OFF Patient Diary, UPDRS, CGI, Patient Global Impression -Improvement (PGI-I) scores, Parkinson's Disease Questionnaire (PDQ), and Medical Outcomes Study 36-item Short Form (SF-36).

6.1.6 Efficacy Findings

Table 6.2-Summary of Results for Primary Outcome Parameter for Istradefylline Pivotal Trials

Study	Primary Outcome	Analysis	Treatment group (n)	Mean Δ from baseline LMS	P value	Any dose
KW6002-US-005	Δ from baseline to end point (wk 12) in % of awake off time	2 way ANOVA	40 mg (129) Placebo (66)	-10.81% -4..04%	0.007	
KW6002-US-006	Δ from baseline in % of awake off time	2-way ANOVA supporting ANCOVA[a]	 20 mg (163) 60 mg (155) Placebo (77)	ANOVA (ANCOVA) -7.72(-7.83) -7.84 (-7.96) -4.07 (-3.47)	ANOVA (ANCOVA) 0.088 (0.026) 0.082 (0.024)	ANOVA (ANCOVA) 0.16 (0.049)
KW6002-US-013	Δ from baseline in % of awake off time	ANCOVA	20 mg (112) Placebo (113)	-9.49% -4.92%	0.025	
KW6002-US-018	Δ from baseline in % of awake off time	ANCOVA	10 mg (149) 20 mg (144) 40 mg (145) Placebo (146)	-6.52% -6.81% -8.97% **-8.31%**	0.319 0.408 0.714	0.475
*KW6002-EU-007 Comparator to entacapone 200 mg Each vs placebo	Δ from baseline in % of awake off time	ANCOVA	40 mg (158) Entacapone 200 mg each dose of LD (146) Placebo (151)	-5.14 -7.82 -4.53	0.729 0.064	

*In Study EU-007 the unadjusted means baseline-endpoint are Placebo= **-4.76,** istradefylline 40 mg= -4.31, entacapone= -7.42, indicating istradefylline is inferior to placebo.

Additional Studies

6002-US-051

Kyowa study 6002-US-051 examined the effects of istradefylline 40 mg/day given as monotherapy in subjects with early (Hoehn & Yahr stage 1-2.5) PD. A total of 176 subjects were randomized, 94 received istradefylline 40 mg/day and 82 received placebo. The primary endpoint selected was improvement at 12 weeks compared to baseline in the UPDRS part III (motor subscale) scores. Key secondary outcome variables selected to evaluate change in motor performance and function were:

- UPDRS Total Score (Subscales I, II, and III), Subscale I score, Subscale II score, and
-
- Subscale IVA score at Weeks 2, 4, 8, 12, and Endpoint;
- CGI-S at Weeks 2, 4, 8, 12, and Endpoint
- Webster Performance Index at Weeks 2, 4, 8, 12, and Endpoint
- Timed Tapping Test at Weeks 2, 4, 8, 12, and Endpoint

The PGI-I (patient global impression of improvement), was analyzed at Weeks 2, 4, 8, 12, and Endpoint.

Efficacy

None of the primary or secondary outcome variables demonstrated a significant between group difference between placebo and istradefylline 40 mg/day. Although, the US-051 study is not a pivotal study supporting the requested indication, the results suggest the clinical effects of istradefylline on motor function are not statistically or clinically significant as monotherapy, in subjects with early PD.

Study 6002-0406

Study Title:

"Placebo-Controlled, Double-Blind, Exploratory Study of KW-6002 (istradefylline) in the Treatment of Parkinson's Disease Adjunctive Therapy to Levodopa".

The was conducted at 13 centers all in Japan. The stated primary objective was to evaluate the efficacy and safety of KW-6002 administered at doses of 20 mg and 40 mg once daily in Parkinson's disease (PD) patients with motor response complications on levodopa therapy. The design was a 12-week, multicenter, placebo-controlled, randomized, double-blind study (Phase 2a, exploratory, parallel-group study). The study population was similar to subjects recruited into the other phase 2b and phase 3 trials. Subjects had advanced PD, Hoehn and Yahr stage 2-4 with motor response fluctuations on levodopa. The primary efficacy variable of this study was the change from baseline to endpoint in the percentage of awake time per day spent in the OFF state, the same as for the phase 2b and 3 trials. The results of the primary efficacy variable failed to show a benefit of any dose of istradefylline over placebo. The LS mean difference in the primary outcome measure demonstrated placebo was superior to all doses of istradefylline tested in the trial.

Study 6002-0406 (Kyowa Table)

Table 11.4.1.1-1 Change from Baseline in the Percentage of Awake Time Per Day Spent in the OFF State Based on Patient's ON/OFF Diary at Endpoint – Observed Case Analysis – Full Analysis Set

			Placebo n=30	20 mg/day n=31	40 mg/day n=28	KW-6002[d] n=59
Baseline	Statistics	n	30	31	28	59
		Mean	39.65	39.04	39.07	39.05
		Std Dev	15.32	16.58	16.90	16.58
		Minimum	13.3	14.7	15.9	14.7
		Median	39.45	41.00	38.60	38.90
		Maximum	80.1	67.3	100.0	100.0
Endpoint - Baseline	Statistics	n	30	31	28	59
		n1[a]	0	0	0	0
		n2[a]	30	31	28	59
		Mean	-8.23	-4.03	-7.66	-6.17
		Std Dev	19.53	12.76	23.27	18.39
		Minimum	-54.8	-34.5	-50.2	-50.2
		Median	-4.10	-4.30	-11.75	-6.20
		Maximum	43.9	18.4	75.5	75.5
	ANCOVA[b]	LS Mean	-8.10	-4.90	-7.72	-6.24
		95%C.I.	-14.72~-1.49	-11.41~1.61	-14.57~-0.87	-10.94~-1.54
		p-value[c]	0.017 *	0.138 NS	0.028 *	0.010 **
	ANCOVA[b] (vs. placebo)	LS Mean	-	3.20	0.38	1.86
		95%C.I.	-	-6.08~12.48	-9.14~9.91	-6.23~9.96
		p-value[c]	-	0.495 NS	0.936 NS	0.648 NS

Unit: %

a) n1, n2 = number of subjects with one or two valid diaries, respectively
b) LS mean and p-value are based on main effects ANCOVA with terms for baseline and treatment (Placebo: 20 mg/day: 40 mg/day or Placebo: KW-6002)

6.1.7 Efficacy Conclusions

Kyowa submitted 5 well controlled, adequately conducted clinical trials to support their NDA application for approval of istradefylline. The data integrity issues concerning data entry of PD diary data from the CRF to the sponsor's electronic data tabulation do not affect the calculation of the primary outcome variable. The handling of duplicate and missing diary entries appear less than ideal but they also did not effect the integrity of the primary outcome variable.

6.1.8 Primary Outcome Measure-Efficacy of the 20 mg dose

Table 6.3-Summary of Clinical Trail Data for The Primary Endpoint at The 20 mg Dose

Study (N)	Support Approval Mean LMS Δ from baseline	Fail to Support Approval Mean LMS Δ from baseline	P value difference compared to placebo
KW6002-US-006 (163)	ANCOVA -7.83%	ANOVA -7.72%	ANOVA (ANCOVA) 0.088 (0.026)
KW6002-US-013 (112)	-9.49%		0.025 ANCOVA
KW6002-US-018 (144)		-6.81%	0.408 ANCOVA
6002-0406 (31)		-4.90%	0.495 ANCOVA

The efficacy of the 20 mg/ day dose of istradefylline clearly demonstrates statistically significant between group difference in the 6002-US-013 trial. In study 6002-US-006, istradefylline fails to demonstrate a statistically significant benefit over placebo for the 20 mg or 60 mg dose, using the pre-specified ANOVA method of analysis. The sponsor presented the results of a pre-specified supporting analysis of the data using an ANCOVA model that demonstrated a statistically significant difference with the placebo treated group at the 20 and 60 mg/day doses. Holding the sponsor to a strict standard means there is only a single study demonstrating efficacy of the 20 mg dose. In discussions with the statistical reviewer and the entire review team the division did not object to considering the ANCOVA model as valid. The 6002-US-018 study was well controlled and sufficiently powered but the 20 mg dose was not superior to placebo for the primary outcome measure, in fact the least mean square difference from the baseline visit to endpoint was greater for the placebo group than it was for the 20 mg istradefylline group. The much smaller 6002-0406 study also failed to demonstrate superiority of istradefylline 20 mg over placebo and again the LMS difference from the baseline visit to endpoint was better in the placebo group.

6.1.9 Primary Outcome Measure-Efficacy of the 40 mg dose

Table 6.4-Summary of Clinical Trail Data for The Primary Endpoint at The 40 mg Dose

Study (N)	Support Approval Mean LMS Δ from baseline	Fail to Support Approval Mean LMS Δ from baseline	P value difference compared to placebo
KW6002-US-005 (129)	-10.81% ANOVA		0.007 ANOVA
KW6002-US-018 (145)		-8.97%	0.714 ANCOVA
KW6002-EU-007 (158)		-5.14%	0.729 ANCOVA
6002-0406 (28)		-7.72%	0.936 ANCOVA

Only the 6002-US-005 study demonstrates efficacy of the 40 mg/day group over placebo. The remaining 4 studies fail demonstrate istradefylline 40 mg/day is superior to placebo based on the primary outcome measure.

6.1.10 The 10mg/day and 60 mg/day Dose of Istradefylline

(b) (4)

Only the 6002-US 006 study examined the 60 mg dose of istradefylline. The results at 60 mg were the same as for the 20 mg dose in that trial, with only the supporting ANCOVA analysis demonstrating superiority over placebo and the primary ANOVA analysis failing to demonstrate a benefit over placebo. The 10 mg/day dose of

istradefylline failed to demonstrate superiority over placebo in both the 6002-US-018 study and in the smaller 6002-0406 study.

6.1.11 Key Secondary Outcome Measures

Table 6.5-P Values For Change From Baseline to Endpoint Compared to Placebo Istradefylline

Study	UPDRS part III ON	UPDRS part III OFF
6002-US-005	40 mg=0.822	0.838
6002-US-006	20 mg=0.462, 60 mg= 0.280	20 mg=0.183, 60 mg=0.294
6002-US-013	20 mg=0.411	
6002-US-018	10 mg=0.572, 20 mg=0.959, 4 40 mg=0.028	
6002-EU-007	*40 mg=0.064, Entacapone =0.043	

*****Entacapone active comparator study both drugs compared to placebo

Table 6.6-CGI Difference from Baseline to Endpoint Istradefylline

Study	CGI-I p value	CGI-S p values	PGI-I p values
6002-US-005	0.326		
6002-US-006	20 mg=0.666, 60 mg=0.136		
6002-US-013		20 mg=0.516	20 mg=0.640
6002-US-018		10 mg=0.678, 20 mg=0.567, 40 mg=0.146	10 mg=0.640 20 mg=0.953 40 mg=0.564
6002-EU-007		40 mg=0.423 *Entacapone=0.71	40 mg=0.16, *Entacapone=0.044

*****Entacapone active comparator study both drugs compared to placebo

Table 6.7-Change from Baseline to Endpoint

Study	PDQ-39 p value	SF-36 p value
6002-US-013	20 mg=0.337	0.370
6002-US-018	10 mg=0.596 20 mg=0.098 40 mg=0.226	*
6002-EU-007	40 mg=0.847 Entacapone=0.340	*

*Only subscales reported total SF-36 scores not reported by sponsor

These yey secondary outcome variable were included in the efficacy summary because these items of interest address how subjects feel or function. The CGI-Improvement or Severity scores did not demonstrate a significant between group difference in any of the five pivotal trials. The CGI is often selected as a co-primary endpoint in trials where the primary endpoint is solely

clinical without an accepted biomarker of change in underlying condition. In all of the pivotal the CGI-I or CGI-S fails to demonstrate a statistically significant difference favoring istradefylline. The ADL and motor portions of the UPDRS fail to demonstrate improvement at doses below 40 mg the effects of the 40 mg/day dose on portions of the UPDRS are inconsistent. In the 6002-US-013, 018 and EU-007 trials, patient rated quality of life measures including the PDQ-39, SF-36 and Patient Global Impression of Improvement (PGI-I) failed to demonstrate a significant difference of istradefylline compared to placebo from baseline to endpoint any dose.

Efficacy Conclusion

Considering the entire body of clinical trials evidence, istradefylline does not demonstrate consistent superiority compared to placebo in subjects with advanced Parkinson's disease at 10 mg, 20 mg or 40 mg/day. Two undisputed supporting trials, one at 20 mg/day and another at 40 mg/day demonstrate statistically significant superiority of istradefylline compared to placebo based on analysis of the primary endpoint. Other clinical trials with nearly identical design, subject characteristic and the same primary endpoint fail to demonstrate efficacy of istradefylline over the entire dose range selected for approval. Istradefylline does not meet the agency standard of two well controlled clinical trials at the 40 mg dose and only meets this standard at the 20 mg/day dose if the results of the supportive ANCOVA analysis in the 6002-US-006 are accepted.

Examination of key secondary endpoints CGI, quality of life measures (PDQ-39, SF-36) and UPDRS data indicates even when statically significant effects of istradefylline is demonstrated using the primary endpoint it is not accompanied by a clinically recognizable effect in global function or quality of life. Istradefylline fails to achieve a statistically significant between group difference, in any of the key secondary outcome measures, in any of the 5 pivotal trials. The data concerning secondary endpoint do not demonstrate subjects feel or function any better on istradefylline compared to placebo.

The opinion of this reviewer is that istradefylline does not meet the agency standards for proving efficacy and it should not be approved for marketing as an adjunctive medication for the treatment of Parkinson's disease in the United States.

7 INTEGRATED REVIEW OF SAFETY (ISS)

7.1 Methods and Findings

The sponsor included data from 15 Phase 2 and 3 studies as the safety database for this application. The data was organized and analyzed in 5 data pools described below. Seven single dose and eight multiple dose studies were included in the integrated summary of safety. Seven phase 1, drug-drug interaction studies were analyzed separately and they were not included in the ISS. Two additional studies performed in special subject populations were excluded from the

ISS. The sponsor's rational for excluding these studies from the ISS are the potential confounding effects of administration of concomitant medications for the drug-drug interaction studies and the effects caused by disease would confound the data in special population trials.

Subjects with idiopathic Parkinson's disease who have had motor response complications with levodopa/carbidopa or levodopa/benserazide therapy:

Pool I: Five Phase 2b/3 double-blind, placebo-controlled fixed-dose studies (Studies 6002-US-005, 6002-US-006, 6002-US-013, 6002-US-018 and 6002-EU-007).

Pool II: Three open-label, long-term exposure studies (Studies 6002-US-007 and 6002-INT-001 final data and interim analysis data from Study 6002-US-025).

Study 6002-US 007 was stopped by Kyowa on September 23, 2003 after a meeting with the FDA concerning brain mineralization discovered in rats during a 2 year carcinogenicity study (KHK/075). A total of 496 subjects were enrolled in the study by the time the sponsor closed the trial because of the potential safety concern raised by the findings observed in rats. The median duration of exposure for subjects in the 6002-US-007 trial before closing was 25 weeks, the longest exposure was 61 weeks. The closing of study 6002-US-007 presented a problem in terms of how to count data from these subjects when calculating exposure, which is discussed in the exposure portion of this review. After determining the observations in rat brains was species specific and the findings were not associated with necrosis or ischemia in rats, human trials resumed. In October 2004, the sponsor initiated study 6002-INT-001, a one-year open label safety trial of 20 mg or 40 mg istradefylline in subjects who participated in an earlier phase 2/3 double-blind trial. Data from study 6002-US-007 was included in pool 2, data from completed study 6002-INT-001 and interim data from 6002-US-025 were included in the 4-month update to the ISS sent to the agency on August 7, 2007.

Pool III: Three double-blind, placebo-controlled, forced dose titration, Phase 2a studies (by combining Studies 6002-US-001, 6002-US-004 and 6002-EU04).

Pool IV: Two Phase 2b studies conducted in subjects with Major Depressive Disorder (combining Studies 6002-US-101 and 6002-US-104).

Pool V: Twelve double-blind, placebo-controlled studies regardless of indication (combination of Pools I, III, IV, and VI [recently completed Studies 6002-US-051 and 6002-US-201]).

Pool VI: Two recently completed Phase 2 studies, 6002-US-051 as monotherapy in Parkinson's disease and 6002-US-201 for Restless Legs Syndrome are included in Pool V summary data as described above. Final clinical study reports for these studies are submitted with this clinical summary update. The subject listings from these studies are included in Appendix 8.H.15.4.

The rational for the pooling of data from the sponsor's clinical trials appears appropriate.

7.1.1 Deaths

There were a total of 33 death across the entire NDA, deaths were expressed by the number of patient years in a given safety pool. The number of incident deaths per patient year of study participation ranged from 0.00 to 0.03 per patient year in controlled clinical trials (pool 5). In long-term clinical trials (pool 2) incident deaths ranged from 0.004 to 0.008 per subject-year of follow up, both incident death rates in pools 5 and 2 were at or below the 0.03 deaths per subject-year incident rate calculated from long-term follow up in the DATATOP cohort[4]. The DATATOP cohort was selected for comparison because the data was also from a controlled clinical trial although the subjects were younger with less advanced PD at the time of trial entry. Poewe[3] reported males with PD had greater mortality than females. The most common causes for death in patients with PD were pneumonia, cardiovascular events, stroke and cancer. Cardiovascular events were the most common cause of death in a population based control group and pneumonia was less likely a cause for death among controls compared to individuals with PD (20% vs. 9%).

Table 7.1-Medical Reviewer's Calculation of Incident Deaths in Pool 5 by Dose

Treatment	N Exposed	Total Exposure Days	Person-years	# Deaths	Deaths/person-yr	Deaths-100 person-yrs
Placebo	926	66172	181.29	4	0.022	2.21
Istradefylline 10 mg/day	153	12182	33.38	1	0.030	3.00
Istradefylline 20 mg/day	466	37036	101.47	1	0.010	0.99
Istradefylline 40 mg/day	741	55426	151.85	2	0.013	1.32
Istradefylline 60 mg/day	155	11619	31.83	0	0.00	0.00
Istradefylline 80 mg/day	12	317	0.87	0	0.00	0.00
Istradefylline 120 mg/day	136	4831	13.24	0	0.00	0.00
Total Istradefylline	1663		332.63	4	0.012	1.20

The sponsor's calculation of incident deaths in safety pool 5 are exactly the same those obtained by this reviewer's independent calculation using the sponsors tabulation datasets.

Table 7.2-Tabular listing of Deaths Among Subjects Receiving Istradefylline in Controlled Phase 2-3 Clinical Trials (pool I)

Trial	INV#/Subject#	Age (yrs)	Sex	Dose (mg)	Time(days from start to death or discontinue	Source	Description
US-005	(b) (6)	72	M	40	73/72	Clinical trial	Unknown-Asthma is listed as the cause of death but the death was unattended and should be listed as unknown (elevated pancreatic enzymes prior to death))
US-005		67	M	40	24	Clinical trial	Cardio-respiratory arrest
US-018		72	M	10	39	Clinical trial	Cardiogenic shock
US-018		61	M	40	58	Clinical trial	Psychosis, Suicide Overdose lithium
US-001		65	M	20	88	Clinical trial	Myocardial Infarction
US-022		39	M	40[a]	30	Clinical trial	Completed Suicide

Table 7.3-Deaths Subjects receiving Placebo or Comparator Drug in Controlled Phase 2-3 Clinical Trials (pool I)

Trial	INV#/Subject#	Age (yrs)	Sex	Dose (mg)	Time (days)	Source	Description
EU-007	(b) (6)	72	M	Placebo	136/115	Clinical Trial	Pneumonia, Muscle rigidity
EU-007		70	F	Entacapone	102	Clinical Trial	Respiratory Distress
EU-007		52	M	Entacapone	32	Clinical Trial	Heat Stroke
US-005		71	F	Placebo	32	Clinical Trial	Pneumonia
US-013		53	M	Placebo	23	Clinical Trial	Sudden Death
US-018		67	F	Placebo	23	Clinical Trial	Mesenteric artery occlusion

POOL II

Data and calculations concerning deaths reported in pool 2 were solely supplied by the sponsor, because the tabulation datasets were not included in the sponsor's submission. The sponsor's data included interim data from on-going trials (6002-US-025) and these data sets are incomplete.

Table 7.4- Incident Deaths in Long-term Clinical Trials (Kyowa Table)

Table 8.H-66 Incidence of Deaths per Subject-Year: Pool II (Cumulative Exposure)

	Istradefylline		
	40 mg/day N=1301	60 mg/day N=284	Total N=1585
Incidence per Subject-Year	0.008	0.004	0.007
Number of Deaths [a]	10	1	11
Number of Subjects	1301	284	1585
Total Subject Years	1238.975	275.446	1514.421

Note: Cumulative exposure analysis combining safety data from completed Studies 6002-US-007, 6002-INT-001 and data from 15 subjects in 6002-US-025 as of the interim 11 August 2006 cut-off for the original NDA who were in the Safety Population of one or more of these long-term studies.

[a] Ten additional deaths from ongoing Study 6002-US-025 have been reported in the Kyowa global drug safety database. Individual subject information regarding 7 of the subjects who died in Study 6002-US-025 and had CRF data retrieved and entered into the study clinical database is found in Appendix 8.H.15.15.

Source: Table S.2.2.8.2.3

Table 7.5-Tabular Listing of Deaths Among Subjects Receiving Istradefylline in Long-Term, Uncontrolled Clinical Trials

Trial	INV#/Subject#	Age (yrs)	Sex	Dose (mg)	Time(days)	Source	Description
INT-001	(b) (6)	48	M	40	383	Clinical trial	Pneumonia Aspiration
INT-001		87	M	40	67	Clinical trial	Sudden Death
INT-001		70	M	20	358	Clinical trial	Pneumonia Aspiration
INT-001		70	M	20	262	Clinical trial	Pneumonia
INT-001		70	M	40	168	Clinical trial	Pneumonia
INT-001		76	F	20	380	Clinical trial	Gastroenteritis
INT-001		71	M	40	279	Clinical trial	Cardio-respiratory Arrest
INT-001		74	M	40	385	Clinical trial	Pneumonia Aspiration
US-007		56	M	40	70	Clinical trial	Acute Myeloid Leukemia
US-007		75	M	20	140	Clinical trial	Cardiac Arrest
US-007		83	M	60	100	Clinical trial	Pneumonia
US-025		79	M	40	69	Clinical trial	Pneumonia, Parkinson's disease
US-025		79	M	40	123	Clinical trial	Gasteroenteritis
US-025		84	F	40	107	Clinical trial	Myocardial Infarction
US-025		64	M	40	235	Clinical trial	Bronchopneumonia
US-025		78	M	40	165	Clinical trial	Pneumonia
US-025		63	M	40	241	Clinical	Respiratory Failure

						trial	
US-025	(b) (6)	67	M	40	122	Clinical trial	Cardio-respiratory Arrest
US-025		74	F	40	485	Clinical Trial	Unknown
US-025		71	F	40	219	Clinical trial	Acutely unresponsive cause of death=Unknown
US-025		70	F	20	174	Clinical trial	Parkinson's disease

7.1.2 Review of Narratives for Subjects Receiving Istradefylline for The Treatment of Advanced Parkinson's disease Pool I

Study US-005-A 12 week randomized, Placebo-controlled, double blind trial of istradefylline 40 mg daily as adjunctive therapy to levodopa.

Subject (b) (6). The subject was a 64 year-old Caucasian man with a significant medical history of asthma and basal ganglia lacunar infarction. He received 40 mg of istradefylline in a blinded fashion and during a schedule visit (day 66) he reported emesis for the 4 day preceding the visit without reporting associated symptoms. He self medicated his symptoms with Emetrol, Advil and Pepto-Bismol. Five days later (day 71) the subject was contacted by phone and he reported persistent vomiting again without other complaints. He was instructed to discontinue study drug and he was seen in clinic for an unscheduled visit with clinical lab testing. His labs were described as "slightly abnormal" for WBCs, platelets, neutrophil, alkaline phosphatase, Trypsin-like immunoreactivity, amylase, lipase and glucose. Attempts to contact the subject by phone were unsuccessful on days 80 and 84. The subject was found deceased in his home by local law enforcement. The estimated time of his demise was 7-10 days prior to discovery by the Sherriff. The death was listed as "unattended", the investigator considered the death unrelated to study drug and considered the death as related to worsening asthma. The subject was found to have an elevated total bilirubin, Trypsin-like immunoreactivity, lipase and amylase at the week 8 (scheduled visit) which increased at the time of the unscheduled visit to levels above the PCS levels. The BUN remained with in the normal range at the week 8 and unscheduled visits 6.1 mmol/L and 5.5 mmol/L respectively (nl=1.4-8.6 mmol/L for males age 18-69). The cause of death was coded inappropriately as related to asthma, although the reviewer suspects the subject had pancreatitis prior to his demise the actual cause remains unknown.
Subjec (b) (6) The subject was a 67 year-old Caucasian man who received 40 mg of istradefylline per day. His relevant past medical history includes gastritis, urinary incontinence and erectile dysfunction. The subject discontinued study medication on day 17 because dyskinesia. On day 24 he suffered a cardiac arrest at home and attempts to resuscitate him were unsuccessful.

Study US-018-A 12 week randomized, double-blind, placebo controlled trial of istradefylline 10 mg, 20 mg or 40 mg daily as adjunctive therapy to levodopa.

Subject (b) (6) -The subject was a 61 year–old Caucasian male who received 40 mg of istradefylline daily. His past medical history was remarkable for traumatic brain injury, affective disorder, hypertension and arthralgia. The was taking lithium carbonate 300 mg/daily and 200 mg ibuprofen prn chronically. Study medication was discontinued on day 7 because of hallucinations and paranoia, he was hospitalized on day 11 because of the psychiatric symptoms. The subject was discharged on day 19 but he was readmitted on day 23 because of a suicide attempt involving multiple medications (but not study drug). He was found to have elevated lithium levels (4.2 unknown units or normal range). The subject had sustained functional impairment following his suicide attempt and he was referred to hospice, where he died on day 58. The event was improperly coded as respiratory failure instead of completed suicide and psychosis as a serious adverse event resulting in hospitalization. Both the initial hospitalization and overdose occurred within 30 days of the subjects exposure to study medication.

Subject (b) (6) A 72 year-old Caucasian man who received istradefylline 10 mg/day. His medical history was significant for coronary artery disease, coronary artery bypass surgery, hypertension, Paget's disease, depression and anxiety. On day 5 of the study the patient complained of poor mobility. Then on day 13 he had X-rays performed for an unknown complaint which revealed lesions (no etiology given) in the distal left femur ans the 2nd or 3rd lumbar vertebrae. Review of the CRF finds the subject had complained of left leg pain during the screening visit. Study medication was discontinued on day 18 because of poor compliance with study visits. The subject was hospitalized on day 21 but the reason did not appear in the sponsor's narrative or in the CRF. On day 38 the subject suddenly collapsed and was hospitalized in the ICU. He had very poor left ventricular dysfunction and expired on day 39 due to cardiogenic shock.

Study INT-001 – A long-term open label safety and tolerability trial of istradefylline 20 mg or 40 mg daily. The date of the first dose was October 8, 2004 and the trial is still on-going.

Subject (b) (6) A 69 year-old Caucasian male started on 40 mg of istradefylline daily but on day 314 the dose was reduced to 20 mg for reasons not stated in the narrative. He was hospitalized on day 338 because of paranoid delusions and study medication was discontinued on day 339. The delusions resolved but his condition continued to deteriorate and the subject was hospitalized on day 352. During this hospitalization, the subject developed a fever caused by aspiration pneumonia. His medical care was changed to palliative care only and he died on day 358.

Subject (b) (6) The subject was a 70 year-old Caucasian man started on istradefylline 40 mg which was reduced on day 14 to 20 mg/day, increased to 40 mg/day on day on day 28, then decreased again to 20 mg/day on day 50. The subject entered the hospital on day 224 for treatment of a hip fracture resulting from a fall. He was discharged to a nursing facility to recover where he developed an acute encephalopathy on day 229. He was readmitted to the hospital for syncope on day 236. Istradefylline was discontinued on the same day. The subject started heparin at some unknown day prior to experiencing syncope. The narrative gives no

additional information until day 262 when the subject died. Post-mortem examination concluded the probable cause of death was confluent pneumonia.

Subject (b) (6) - The subject was an 87 year-old Caucasian male who received istradefylline 40 mg/day. His past medical history was significant for coronary artery disease, coronary artery bypass surgery, enterococcal endocarditis and aortic valve replacement, left bundle branch block, abdominal aortic aneurysm, chronic pneumonia, hallucinations arthritis, hypothyroidism, and anemia. On day 67 the patient died at home narrative did not mention signs of new illness or adverse experience. An autopsy was not performed and the cause of death was unknown to the investigator.

Subject (b) (6) - A 48 year-old male who's' ethnicity was Japanese and Portuguese. His medical history was remarkable for Dysphagia and aspiration pneumonia requiring a feeding tube. The subject was initially maintained on istradefylline 40 mg but on day 15 this was reduced to 20 for reasons that were not reported in the narrative. On days 86-282 his istradefylline dose was increased back to 40 mg. on day 269 the subject reported chest and arm pain and was sent to the emergency room. He was treated for aspiration pneumonia and despite some improvement study drug was discontinued on day 282 because the subject could no longer take oral medications. On day 284, he was transferred for rehabilitation in a long-term care facility but he still received antibiotics. The patient died approximately 2 months later on day 338.

Subject (b) (6) A 70 year-old Hispanic man who received 40 mg of istradefylline/day. On day 164 the patient developed fever and dyspnea and he was admitted to the hospital for treatment of pneumonia. The subjects medical condition worsened despite treatment and he died on day 168.

Subject (b) (6) A 75 year-old Asian woman who received istradefylline 40 mg daily which was reduced to 20 mg on day 15. Besides Parkinson's disease the subjects medical history was remarkable only for hypertension. Study medication was discontinued on day 376 of the study for reasons that were not documented in the narrative or CRF. The reason for withdrawal form the study medication is presumed due to gastroenteritis described a "medically significant" which was first reported on day 377. The subject expired on day 380 in hospital, no autopsy was performed.

Subject (b) (6) A 71 year-old Asian man who received 40 mg of istradefylline daily. Treatment with study medication was interrupted from days 139-169 because of pneumonia. The subject fell on day 125 for a right comminuted fracture of the right femur treated with traction. The subject was discharged on day 128 but was re hospitalized on day 129 because of hematemesis, melena and pneumonia due to Mallory-Weiss syndrome. The subject was discharged form hospital on 163 but he was unwilling to continue study medication. The final study visit was conducted on day 212. The investigator reported the subject died at home after lapsing into a "moribund state" on day 279 (2 months after he discontinued study medication).

Subject (b) (6) - A 73 year-old Asian man who received istradefylline 40 mg. His medical history was significant for hypertension, peripheral neuropathy diabetes mellitus and surgery for

a herniated disk. The subject developed dysphagia with difficulty breathing. The subject was cared for at home and the subject's family refused hospitalization. The subject died two days (study day 385), 20 days after completing the study. The cause of death was presumed to be aspiration pneumonia.

Study US-007 (a long-term, open label, flexible dose trial of 20 mg, 40, mg or 60 mg istradefylline daily)

Subject (b) (6) - A56 year-old Caucasian man who completed a previous double blind study of istradefylline, study US-005. At the subject was reported to have low WBC and platelet counts through out the US005 study. The subject received istradefylline 40 mg during the US-005 study. His WBC and platelet count were low at the screening visit in the US-005 study but remained stable [PLT 56-63X10^9/L (low limit=140 X10^9/L), WBC 0.84-1.73X10^9/L (low limit 3.8X10^9/L)]. Despite a low WBC (0.84X10^9/L) at the US-007 screening visit the subject enrolled in the study and received istradefylline 40 mg. He withdrew from the study on day 22. He a bone marrow aspiration on day 33 which revealed changes consistent with acute myeloid leukemia. The subject underwent chemotherapy but developed aplastic anemia approximately on day 54. Hepatic failure developed due to hepatic veno-occlusive disease and the subject dies on day 70 due to multiple organ system failure. The cause of death was a result of acute myeloid leukemia.

Subject (b) (6) – A75 year-old Caucasian man treated in istradefylline 40 mg/day in the open label US-007 study and he received istradefylline in a previous double blind study of istradefylline. His medical history was remarkable for stroke, malignant melanoma, glaucoma and gastrointestinal reflux. On day 49 of study medication the patient developed difficulty breathing. He was hospitalized n day 52 because of Dyspnea and dyspahgia. A swallowing evaluation was completed on day 55 and chest X-ray did not reveal pneumonia. The patient continued study medication until the subject withdrew consent on day 130. The subject elected to have Deep Brian Stimulation surgery on day 133 for treatment of his Parkinson's symptoms. He suffered respiratory arrest followed by cardiac arrest and died on day 140.

Subject (b) (6) - A 83 year-old Caucasian man who received 60 mg of istradefylline in this open label study. He also received istradefylline during his participation in US-006, a 12-week, double-blind trial that preceded the US-007 trial. His medical history was significant for orthostatic hypotension, pneumonia, bradycardia peptic ulcer disease and spinal stenosis. On day 91 the subject started treatment for pneumonia and he withdrew from the study on the same day. The subject was admitted to the hospital on day 97 where chest X-ray confirmed pneumonia affecting the left lower lobe of the lung. The patient expired on day 100.
Study 6002-US-025 (a long-term study of patients who continue beyond 52 weeks in the INT-001 in this open label flexible dose study of 20 mg or 40 mg of istradefylline/day).

Subject (b) (6) - A79 year-old Caucasian man who received istradefylline 40 mg/day. His medical history is significant for dysphagia, macular degeneration, cataract, deafness, angina, hypotension, congestive heart failure chronic obstructive pulmonary disease and gastroesophageal reflux. The subject stopped all medications including study drug on an

undisclosed date and entered hospice care. The subject attending his screening visit on (b) (6) and died on (b) (6).

Subject (b) (6) - A 79-year-old Caucasian man who received istradefylline 40 mg/day. He was hospitalized on day 123 because of nausea and vomiting. The subject was hospitalized and was found to have a small bowel obstruction due to an incarcerated right inguinal hernia. The subject experienced an episode of severe nausea and vomiting resulting in bilateral aspiration pneumonia. The patient died on study day 131 the cause of death was listed as gastroenteritis, no autopsy was performed.

Subject (b) (6) - An 84-year-old Caucasian female who received istradefylline 40 mg/day. Her relevant medical history was remarkable for hypertension, gastroesophageal reflux, kyphoscoliosis, balance disorder, arthritis and Raynaud's phenomenon. The subject was admitted to the hospital for surgery to correct severe kyphoscoliosis. Prior to surgery the patient discontinued study medication on day 103. Intra-operatively the subject experienced two episodes of wide complex tachycardia and one episode of narrow complex tachycardia. On post-operative day three the subject complained chest pain and lost consciousness. The subject had ventricular tachycardia with, sinus rhythm was reestablished but she remained unresponsive. ECG changes were consistent with an acute anteriolateral myocardial infarction and the subject died on day 107 without regaining consciousness.

Subject (b) (6) - A 64-year-old Caucasian man who was treated with istradefylline 40 mg/day. His relevant medical history was remarkable for Angina, hypertension, pericarditis, transient ischemic attacks, anxiety, depression, psychotic disorder. On day 232 of the study the subject developed chest congestion and possible aspiration pneumonia. The subject died 3 days later with "chronic kidney tract infection" listed an a contributing cause of death along with pneumonia.

Subject (b) (6) - A 78-year-old Caucasian man who received istradefylline 40 mg/day. His relevant medical history was remarkable for myocardial infarction, angina, coronary artery stent placement, hypertension, lung nodule, recurrent prostate cancer, hypothyroidism and gastroesophageal reflux, deep venous thrombosis. Concomitant medications of importance include Warfarin "25 mg" daily and quetiapine 450 mg/day. The subject experienced generalized weakness on day 104 of the study. On day 112 the subject had clinical lab work performed as part of a scheduled study visit, multiple lab abnormalities were found but specific values were not reported. The subject was admitted to the hospital on day 118 and received 4 units of red blood cells over the next 6 days. On day 125 the subject was discharged to hospice care, study medication was stopped on day 147 and the subject died on day 148. The causes of death listed for the subject were renal insufficiency, dehydration and anemia.

Subject - (b) (6) - A 63 year-old Caucasian man who received istradefylline 40 mg/day. His pertinent medical history includes paranoia, chronic back and limb pain, lumbar vertebral fracture and cognitive disorder. On day 241 of the study the subject was residing in a nursing facility, the staff found him in his wheelchair experiencing respiratory distress. Emergency services were called but the subject died at the scene.

Subject (b) (6) A 67-year-old Caucasian man treated with istradefylline 40 mg/day. His medical history was significant for myocardial infarction, transient ischemic attack, syncope, renal insufficiency, and hypertension. On day 138 the subject went hiking, late in the day he was found unresponsive and pulseless. He was resuscitated and taken to the hospital were he died on day 139. The cause of death was unknown and autopsy was not preformed.

Subject (b) (6) - A 73 year old Caucasian woman received with istradefylline 40 mg/day. Her pertinent medical history was remarkable for cardiac disorder, increased muscle enzymes and drug hypersensitivity. The subjects reported she died in her sleep on (b) (6). The sponsor did not include information concerning duration of treatment or information from the last recorded study visit.

Subjec (b) (6) - A 71-year-old Caucasian woman treated with istradefylline 40 mg/day. Her medical history was remarkable for hypertension and drug hypersensitivity. On day 216 of the study the subject was scheduled to receive a C.T. scan of her head fro reasons that were not reported. She suddenly became unresponsive but improved shortly after hospitalization. While the subject was hospitalized she fell and fractured her pelvis. Her pain was treated with Demerol which caused increasing confusion. On day 219 the subject became suddenly confused and developed respiratory distress. The subject developed seizure activity and was treated with midazolam, morphine and furosemide. She remained unresponsive and died. There was no mention of an autopsy and the cause of death remains unknown.

Subject (b) (6) - A 70-year-old Caucasian female who received 20 mg of istradefylline daily. Her medical history was significant for urinary tract infection and drug hypersensitivity. The subject fell and sustained a hip fracture on (b) (6). The subject died on day 174 of the study with no further details.

Study -002-US-001 (A 1-year open label of 20 mg or 40 mg of istradefylline in subjects with Parkinson's disease and motor response complication on levodopa).

Subjec (b) (6) A 65-year-old Caucasian man who started istradefylline on (b) (6). His medical history was significant for atrial fibrillation and hypertension. Atrial fibrillation was recorded at study visits 4,8 and 12 weeks respectively. Study medication was discontinued on (b) (6) one day after seeing his cardiologist. On (b) (6) he was prescribed a salbutamol inhaler because of persistent respiratory difficulty. On (b) (6) (day 88) the subject suffered an acute myocardial infarction and died. Mild elevations <1.5X ULN of percent neutrophils, fasting glucose, creatinine, urea urine protein and lipase were reported as clinically significant by the site investigator, none were related to the patients myocardial infarction or appeared to relate to the subjects respiratory problems.

Study-6002-US-022 (A single dose study in healthy volunteers of istradefylline 40 mg).

Subject (b) (6) - A 39-year-old African American man received a single dose of istradefylline on (b) (6) and again on (b) (6). He was discharged from study related confinement ion an in-patient monitoring unit. He was discharged on (b) (6). He

had a history of incarceration for criminal behavior and an arrest warrant was issued prior to his death because of repeated parole violations. On the day of discharge from study related in-patient confinement, the subject committed suicide by self-inflicted gunshot wound.

Reviewer's Conclusions

Overall, the placebo group reported a higher number of incident deaths compared to the total istradefylline treated group in the long-term safety studies. The only dose of istradefylline with a higher rate of incident death was the 10 mg group. Exposure was limited for the 10 mg dose, which is a low dose use only for titration on the way up to higher doses. There was only a single death reported in the 10 mg group with a relatively low exposure causing a spuriously high incident death rate.

There did not appear to be significant differences in the number and listed cause of death for subjects who received istradefylline compared to those who received placebo. In cases where this reviewer did not agree with the listed cause of death there was not enough information known to establish a cause of death with certainty.

7.1.3 Other Serious Adverse Events

7.1.4 Serious Adverse Events Pool I

A comparison of the sponsor's analysis of other serious adverse events in pool I with the results obtained using the MAED data mining software of adverse events found there was no significant differences in the results. There was no evidence found suggesting a significant drug related serious adverse event that distinguished itself from the placebo group. Additional analysis performed by the MAED data mining tool included grouping of the preferred terms to higher level terms, higher level group terms and system organ class. The grouping of the preferred terms did not reveal evidence of a trend in the other serious adverse events. Standardized MedDRA Queries (SMQs) were conducted using broad and narrow criteria. SMQ analysis did not identify a significant difference in serious adverse events between the placebo and istradefylline groups in pool I

Table 7.6-The Sponsors Tabulation of Other Serious Adverse Events in Pool I

Table 8.H-40 Overview Summary of TEAEs: Pool I

Subjects	Number (%) of Subjects					
		Istradefylline				
	Placebo N=561	10 mg/day N=153	20 mg/day N=427	40 mg/day N=440	60 mg/day N=155	Total N=1175
Subjects with any TEAE	**413 (73.6)**	**126 (82.4)**	**346 (81.0)**	**346 (78.6)**	**133 (85.8)**	**951 (80.9)**
Subjects with serious TEAE	19 (3.4)	6 (3.9)	19 (4.4)	23 (5.2)	4 (2.6)	52 (4.4)
Subjects with any TEAE leading to discontinuation	33 (5.9)	5 (3.3)	27 (6.3)	30 (6.8)	16 (10.3)	78 (6.6)
Subjects with any related [a] TEAE	285 (50.8)	93 (60.8)	243 (56.9)	251 (57.0)	98 (63.2)	685 (58.3)
Subjects with any severe TEAE	58 (10.3)	18 (11.8)	51 (11.9)	56 (12.7)	19 (12.3)	144 (12.3)
Deaths	4 (0.7)	1 (0.7)	0	2 (0.5)[b]	0	3 (0.3)

[a] Related = includes probably and possibly study drug related.
[b] Subject (b) (6) in Study 6002-US-018 who died 52 days after the last dose of study drug, is not included.
Source: Table S.2.2.1.1

Table 7.7-Reviewer's Analysis Pool 1 of Other Serious Adverse Events (MAED)

MedDRA 7.0 PREFERRED TERM	Placebo	Entacapone 200 mg	Istradefylline 10 mg/day	Istradefylline 20 mg/day	Istradefylline 40 mg/day	Istradefylline 60 mg/day
Number Exposed	(N=564)	(N=154)	(N=155)	(N=428)	(N=441)	(N=155)
TOTAL SUBJECTS WITH MORE THAN ONE EVENT	21 (3.7%)	5 (3.2%)	6 (3.9%)	19 (4.4%)	25 (5.7%)	6 (3.9%)
CORONARY ARTERY DISEASE	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
URINARY TRACT INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)
ACCIDENT	1 (0.2%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	4 (0.9%)	0 (0.0%)
CHEST PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)
LOSS OF CONSCIOUSNESS	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
HIP FRACTURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	1 (0.2%)	1 (0.6%)
RIB FRACTURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	2 (0.5%)	0 (0.0%)
PNEUMONIA	3 (0 5%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.2%)	1 (0.6%)
PARKINSON'S DISEASE	1 (0.2%)	0 (0.0%)	1 (0.6%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
FALL	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	1 (0.2%)	1 (0.6%)
ASTHMA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
CARDIAC FAILURE CONGESTIVE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
PSYCHOTIC DISORDER	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
HUMERUS FRACTURE	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)

CARDIO-RESPIRATORY ARREST	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
CONFUSIONAL STATE	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)

Pool V

Analysis of SAE data for pool using the MAED data mining software did not reveal a significant difference between the sponsor's and reviewer's analysis for serious adverse events. The number and type of SAE reported appeared similar for the placebo and istradefylline treated groups in pool V. Additional analysis performed by the MAED data mining tool included grouping the preferred terms to higher level terms, higher level group terms and to system organ class. Grouping of the preferred terms did not reveal additional istradefylline related SAEs. Standardized MedDRA Queries (SMQ) were conducted using broad and narrow criteria and again there were no significant serious adverse events in pool V identified on the basis of the SMQ analysis.

Table 7.8-The sponsor's Analysis of SAE Pool V

Table 8.H-44 Overview Summary of TEAEs: Pool V

	Number (%) of Subjects							
		Istradefylline						
Subjects	Placebo N=927	10 mg/day[a] N=153	20 mg/day[a] N=467	40 mg/day[a] N=742	60 mg/day[a] N=155	80 mg/day[a] N=12	120 mg/day[a] N=141	Total N=1670
Subjects with any TEAE	**646 (69.7)**	**126 (82.4)**	**379 (81.2)**	**530 (71.4)**	**133 (85.8)**	**7 (58.3)**	**99 (70.2)**	**1274 (76.3)**
Subjects with any serious TEAE	24 (2.6)	6 (3.9)	20 (4.3)	26 (3.5)	4 (2.6)	2 (16.7)	1 (0.7)	59 (3.5)
Subjects with any TEAE leading to discontinuation	52 (5.6)	5 (3.3)	31 (6.6)	47 (6.3)	16 (10.3)	0	8 (5.7)	107 (6.4)
Subjects with any related[b] TEAE	426 (46.0)	93 (60.8)	268 (57.4)	371 (50.0)	98 (63.2)	5 (41.7)	60 (42.6)	895 (53.6)
Subjects with any severe TEAE	80 (8.6)	18 (11.8)	56 (12.0)	80 (10.8)	19 (12.3)	4 (33.3)	17 (12.1)	194 (11.6)
Deaths	4 (0.4)	1 (0.7)	1 (0.2)	2 (0.3)	0	0	0	4 (0.2)

[a] Based on the maximum intended dose during the study.
[b] Related = includes probably and possibly study drug related.
Source: Table S.2.2.1.5

Table 7.9-Reviewer's Analysis of SAE Pool V (Preferred Terms)

Preferred Term	Placebo	Istradefylline					
(MedDRA v7-0)	(N=935)	10 mg/day (N=155)	20 mg/day (N=468)	40 mg/day (N=746)	60 mg/day (N=155)	80 mg/day (N=12)	120 mg/day (N=142)
AT LEAST ONE EVENT	28 (3.0%)	6 (3.9%)	20 (4.3%)	29 (3.9%)	6 (3.9%)	4 (33.3%)	2 (1.4%)
ATRIAL FIBRILLATION	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (8.3%)	0 (0.0%)
CHEST DISCOMFORT	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)
LOSS OF CONSCIOUSNESS	0 (0.0%)	1 (0.6%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANAEMIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HIP FRACTURE	0 (0.0%)	0 (0.0%)	2 (0.4%)	1 (0.1%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
ACCIDENT	1 (0.1%)	1 (0.6%)	0 (0.0%)	4 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
URINARY TRACT INFECTION	0 (0.0%)	0 (0.0%)	2 (0.4%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

CORONARY ARTERY DISEASE	3 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PNEUMONIA	4 (0.4%)	1 (0.6%)	0 (0.0%)	1 (0.1%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
CHEST PAIN	1 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
FALL	1 (0.1%)	0 (0.0%)	2 (0.4%)	1 (0.1%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
DYSKINESIA	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RIB FRACTURE	0 (0.0%)	0 (0.0%)	1 (0.2%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PARKINSON'S DISEASE	1 (0.1%)	1 (0.6%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ASTHMA	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIAC FAILURE CONGESTIVE	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MYOCARDIAL INFARCTION	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PSYCHOTIC DISORDER	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HYPERTENSION	1 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PNEUMONIA ASPIRATION	1 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CONFUSIONAL STATE	1 (0.1%)	0 (0.0%)	1 (0.2%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HUMERUS FRACTURE	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CARDIO-RESPIRATORY ARREST	1 (0.1%)	0 (0.0%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

7.1.5 Dropouts and Other Significant Adverse Events

7.1.5.1 Overall profile of dropouts

The percentage of patients who dropped out of placebo controlled trials because of an adverse event were similar for subjects treated with istradefylline 20 mg/day and 40 mg/day and placebo at approximately 6 %. The overall percentage of subjects who withdrew from clinical trials in the istradefylline 20 mg and 40 mg groups was also similar to group treated with placebo. The subjects treated with 60 mg/day of istradefylline withdrew from clinical trials because of an AE greater percentage 10% but the percentage of subjects reporting any AE in the 60 mg/day group was also higher at 18%. The proportion of subjects who withdrew because of an AE compared to the percentage of subjects reporting AE was similar in all dose groups suggesting the higher doses of istradefylline is not associated with an increased likelihood of an AE being a serious.

Figure 7.1-Percent of Subjects Who Withdrew For Any Reason Compared To Percent Withdrawal Due to AE

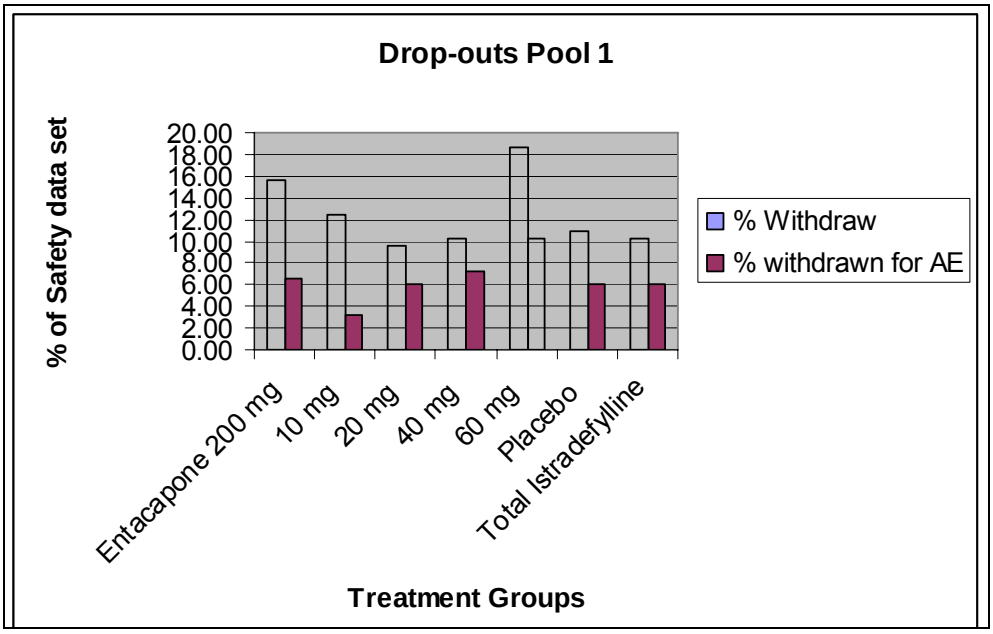


Table 7.10-Reviewer's Analysis of Subjects in Pool 1 who Discontinued Participation

	Treatment						
Reason for Withdraw	**Entacapone 200 mg**	**10 mg**	**20 mg**	**40 mg**	**60 mg**	**Placebo**	**Total Istradefylline**
1 Lack of efficacy	1	2	2	3	2	5	14
2 AE	10	5	26	32	16	34	113
3 Protocol violation	0	4	9	1	5	5	24
4 Consent withdrawn	6	6	3	7	3	13	32
99 other	7	2	1	2	3	4	12
Totals							
Withdrawn	24	19	41	45	29	61	195
N=Safety Set	153	153	427	440	155	561	1889
% Withdrawn	15.69	12.42	9.60	10.23	18.71	10.87	10.32
% Withdrawn for AE	6.54	**3.27**	**6.09**	**7.27**	**10.32**	6.06	5.98

7.1.6 Discontinued For "Other" Reason

Further investigation of the twelve subjects listed as "(99) other" as the reason given for the subject discontinuing participation in the trial revealed:

- Five were listed "as lost to follow-up, two were assigned to the 10 mg Istradefylline group and one was assigned to the placebo group.
- Three subjects were non-compliant with study visits or procedures (diary completion), one each in the istradefylline 20 mg, 40 mg and placebo groups.
- One subject discontinued istradefylline 60 mg after scheduling Deep Brain Stimulation for dyskinesia.
- One subject in the placebo group withdrew for lack of efficacy.
- One subject withdrew for "worsening in his general condition".
- One subject withdrew because they "did not feel right on the medication".

Further investigation did not reveal information that suggested new or serious AEs were classified as "other (99)".

7.1.7 Adverse events associated with dropouts

Dyskinesia, worsening Parkinson's symptoms and nausea were the most common adverse events associated with withdrawal from pivotal clinical trials. Elevation of hepatic enzymes as a reason for discontinuing was more common in the istradefylline groups. These cases are discussed in detail in the discussion of remarkable safety events for individual study.

POOL I Placebo Controlled Clinical Trials Number of Subjects Withdrawn From Study Medication For Any Reason

AE Code	N	Placebo	Entacap	Istrad 10 mg	Istrad 20 mg	Istrad 40 mg	Istrad 60 mg
ABDOMINAL PAIN	2	1					1
ACCIDENT	1				1		
ADENOCARCINOMA	1				1		
AGITATION	1					1	
ALDOLASE INCREASED	1						1
AMNESIA	1	1					
ANGINA PECTORIS	1					1	
ANGINA UNSTABLE	1		1				
ANOREXIA	1	1					
ANXIETY	2				1	1	
ARTHRALGIA	2					1	1
ASTHENIA	1					1	
ASTHMA	1					1	
ATRIAL FIBRILLATION	3	1	1		1		
BACK PAIN	2				1		1
BALANCE DISORDER	1	1					
BLOOD BILIRUBIN INCREASED	1						1
BLOOD CREATINE PHOSPHOKINASE INCREASED	3				1	1	1
BLOOD LACTATE DEHYDROGENASE INCREASED	1						1
BRADYKINESIA	2	1				1	

BUNDLE BRANCH BLOCK LEFT	1	1					
BUNDLE BRANCH BLOCK RIGHT	1	1					
BURNING SENSATION	1		1				
CARDIAC FAILURE CONGESTIVE	1				1		
CARDIO-RESPIRATORY ARREST	2	1			1		
CEREBROVASCULAR ACCIDENT	1	1					
CHEST DISCOMFORT	1				1		
CHEST PAIN	2					2	
CONFUSIONAL STATE	3	1		1		1	
CONSTIPATION	2			1		1	
COR PULMONALE	1	1					
DIARRHOEA	2	1	1				
DISTURBANCE IN ATTENTION	1						1
DIZZINESS	2	1				1	
DRUG INEFFECTIVE	1					1	
DYSARTHRIA	1				1		
DYSKINESIA	20	3	2		2	6	7
DYSPHAGIA	1		1				
DYSTONIA	1					1	
ELECTROCARDIOGRAM T WAVE ABNORMAL	1	1					
FALL	1						1
FEELING ABNORMAL	1				1		
FREEZING PHENOMENON	2				1		1
GAIT ABNORMAL	1						1
GASTRIC IRRITATION	1					1	
HALLUCINATION	2				1	1	
HALLUCINATION, VISUAL	1					1	
HEADACHE	2	1				1	
HEPATIC ENZYME INCREASED	6	1			1	2	2
HIP FRACTURE	2					1	1
HYPOTENSION	1	1					
INSOMNIA	3	2		1			
INTRAOCULAR PRESSURE TEST	1	1					
ISCHAEMIA	1					1	
JOINT SWELLING	1	1					
LETHARGY	1	1					
LEUKOPENIA	1	1					
LIGHTHEADEDNESS	1	1					
LIPASE INCREASED	1				1		
LOSS OF CONSCIOUSNESS	1				1		
MEMORY IMPAIRMENT	2		1		1		
MOTOR DYSFUNCTION	1					1	
MUSCLE CRAMP	1						1
MUSCLE RIGIDITY	5	1	1		1	2	
MUSCLE SPASMS	1				1		
MUSCLE SPASTICITY	1	1					
NAUSEA	9	1		1	1	2	4

NEUTROPENIA	1	1					
ORTHOSTATIC HYPOTENSION	1				1		
OVERDOSE	1				1		
PAIN IN EXTREMITY	1					1	
PALPITATIONS	1				1		
PANCREATITIS	1					1	
PARKINSON'S DISEASE	15	8		1	3	2	1
PNEUMONIA	1	1					
PSYCHOTIC DISORDER	3		1		1	1	
RASH	1				1		
RASH MACULO-PAPULAR	1	1					
RENAL FAILURE ACUTE	1						1
SLEEP DISORDER	1					1	
SOMNOLENCE	2	1				1	
SUDDEN DEATH	1	1					
TREMOR	4	2				1	1
URINARY TRACT INFECTION	1				1		
UROSEPSIS	1				1		
VERTIGO	1						1
VOMITING	1					1	
Total number discontinued study medication=	166	46	10	5	32	43	30

7.1.8 Common Adverse Events

7.1.8.1 Eliciting adverse events data in the development program

Adverse events were elicited during study visits by study site personnel who asked open-ended questions concerning how subjects felt since their last encounter. Instructions were given to study personnel to record detailed information about the AE on the corresponding forms regardless of whether they though the AE was related to the study medication. The sponsor requested investigators follow all AEs until a "satisfactory clinical resolution was achieved". Serious adverse events were defined according to establish criteria, study sites were instructed to report serious events to the sponsor with in 24 hours. Criteria for reporting severity of the individual AEs and their possible relationship to study medication were defined by the sponsor but this was ultimately decided but the site investigator.

A review of the sponsor's analysis of common adverse events was similar to the results this reviewer obtained using the MAED Adverse event data mining software. Nausea and dyskinesia are the most common adverse events, nausea was nearly 3 times more common in the 60 mg/day group compared to any other dose of istradefylline. Orthostatic hypotension was reported in the placebo and the istradefylline treated groups. The number of AEs reported under hypotension or orthostatic hypotension did not reveal a relationship to dose. Somnolence was slightly more frequent in the placebo treated group. Hallucinations were more frequent in the istradefylline treated group, increasing slightly as the dose of istradefylline increased.

Parkinson's symptoms was reported most frequently in the group that received istradefylline 10 mg but they were smaller in number compared to the other dose groups.

7.1.8.2 Appropriateness of adverse event categorization and preferred terms

The sponsor's grouping of preferred terms to MedDRA higher level, higher level group terms and system organ class appeared appropriate across all of the pivotal trials. This reviewer compared the sponsor's analysis of SAEs grouped by system organ class to results obtained from the MAED data mining software and found the results were nearly identical. The sponsor's method of grouping the preferred terms to HLT, HLGT and SOC appear appropriate.

7.1.8.3 Incidence of common adverse events

7.1.8.4 Common adverse event tables

Table 7.11-Reviewers Analysis of Common AEs in Placebo Controlled Trials (Pool I) By Preferred Terms (occurring more once) (MAED)

	Placebo	Istradefylline 10 mg/day	Istradefylline 20 mg/day	Istradefylline 40 mg/day	Istradefylline 60 mg/day
	N=564	N=155	N=428	N=441	N=155)
AT LEAST ONE EVENT	414(73.4%)	126 (81.3%)	346 (80.8%)	347 (78.7%)	133 (85.8%)
NAUSEA	37 (6.6%)	11 (7.1%)	38 (8.9%)	35 (7.9%)	35 (22.6%)
DYSKINESIA	75 (13.3%)	33 (21.3%)	91 (21.3%)	102 (23.1%)	37 (23.9%)
HYPOTENSION	3 (0.5%)	2 (1.3%)	2 (0.5%)	0 (0.0%)	0 (0.0%)
JOINT STIFFNESS	1 (0.2%)	3 (1.9%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
ABNORMAL DREAMS	3 (0.5%)	5 (3.2%)	11 (2.6%)	7 (1.6%)	8 (5.2%)
WEIGHT FLUCTUATION	32 (5.7%)	6 (3.9%)	28 (6.5%)	27 (6.1%)	2 (1.3%)
CONSTIPATION	21 (3.7%)	10 (6.5%)	33 (7.7%)	28 (6.3%)	3 (1.9%)
HALLUCINATION	15 (2.7%)	2 (1.3%)	13 (3.0%)	16 (3.6%)	9 (5.8%)
CONFUSIONAL STATE	2 (0.4%)	5 (3.2%)	5 (1.2%)	3 (0.7%)	2 (1.3%)
HOT FLUSH	7 (1.2%)	3 (1.9%)	0 (0.0%)	3 (0.7%)	0 (0.0%)
MONOARTHRITIS	0 (0.0%)	2 (1.3%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
PARKINSON'S DISEASE	35 (6.2%)	17 (11.0%)	26 (6.1%)	21 (4.8%)	5 (3.2%)
LIPIDS INCREASED	1 (0.2%)	2 (1.3%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
EXCORIATION	4 (0.7%)	2 (1.3%)	2 (0.5%)	0 (0.0%)	3 (1.9%)
ACCIDENT	26 (4.6%)	9 (5.8%)	16 (3.7%)	19 (4.3%)	1 (0.6%)
OEDEMA PERIPHERAL	19 (3.4%)	2 (1.3%)	14 (3.3%)	12 (2.7%)	4 (2.6%)
DYSTONIA	4 (0.7%)	2 (1.3%)	1 (0.2%)	7 (1.6%)	2 (1.3%)
RASH	8 (1.4%)	3 (1.9%)	9 (2.1%)	9 (2.0%)	2 (1.3%)
ORTHOSTATIC HYPOTENSION	7 (1.2%)	2 (1.3%)	4 (0.9%)	2 (0.5%)	0 (0.0%)
SOMNOLENCE	21 (3.7%)	5 (3.2%)	12 (2.8%)	10 (2.3%)	4 (2.6%)
FREEZING PHENOMENON	11 (2.0%)	4 (2.6%)	9 (2.1%)	10 (2.3%)	3 (1.9%)

Identifying Common and Drug-Related Adverse Events

Reviewer Comment

The frequency of TEAEs was greater in the istradefylline treated groups compared to placebo. Results of this reviewer's independent analysis of common TEAEs using the MAED software was similar to the sponsor's analysis of common AEs for Pool I. Nausea was most frequently reported as an AE in the istradefylline 60 mg/day group but doses below 60 mg were only slightly higher than placebo. Dyskinesia was also more common in all of the istradefylline treated groups and the frequency of reporting as an AE was similar for all of the dose group. Hallucinations were slightly more frequent in all of the istradefylline treated groups compared to placebo with evidence of a dose response relationship that was small.

7.1.8.5 Additional analyses and explorations

Impulse Control Disorders

Impulse control disorders (ICD) is associated with many dopaminergic medications, although the cause effect relationship is not clear and the potential for disease-medication may be significant. The ICDs are disruptive and cause distress among patients with PD and their caregivers. Commonly recognized ICDs are increased libido/hypersexuality, obsessive-compulsive behaviors including eating, compulsive gambling but there are other ICD as well. Frequency estimates of ICDs in patients taking dopaminergic medications are based post-marketing data. Data concerning ICDs in clinical trials involving subjects with PD receiving dopaminergic medications is only beginning to be studied systematically. Specific information concerning ICD, active surveillance, questionnaires or structured interviews were not included in the protocol designs for the pivotal clinical trials of istradefylline. The issue of ICDs in patients with PD was not a recognized area of concern until after the trials for istradefylline were nearly completed.

ICDs Pool I (Controlled Trials for Parkinson's)

Pool I data examines subjects with PD in controlled clinical trials. Although, there relatively few cases of compulsive gambling reported in Pool I, both of the cases occurred in subjects taking istradefylline and none were reported in subjects in the placebo group. The same pattern of AE reports occurring only in the istradefylline group for obsessive/compulsive behavior (OCB) but there were no AE reports of hypersexuality or increased libido.

Table 7.12-Compulsive Gambling Pool 1

I.D.	Age	Sex	Drug/Dose	AE Term	Serious	Outcome
(b) (6)	56	M	Istradefylline 20 mg/day	COMPULSIVE GAMBLING	N	Resolved
	60	F	Istradefylline 20 mg/day	COMPULSIVE GAMBLING	N	Ongoing

*None reported in placebo group

Table 7.13-Obsessive/Compulsive Behavior Pool 1

USUBJID	AGE	SEX	TRMAXGRP	AETERM	Serious	Outcome
(b) (6)	43	M	Istradefylline 20 mg/day	EXACERBATION OF COMPULSIVITY	N	Resolved
	46	M	Istradefylline 10 mg/day	COMPULSIVE BEHAVIOR	N	Resolved

*None reported in placebo group. 2 subjects with obsessive thoughts were excluded

Impulse Control Disorders Pool V (Controlled trials regardless of indication)

Pool V included data from pool I, analysis of Pool V only uncovered the same cases of compulsive gambling and obsessive-compulsive behaviors reported in pool I (PD studies), there were no additional cases of either AE reported in the other data pools contained in pool V. This suggests that the association of istradefylline's association with ICDs may be specific to PD. All of the cases of increased sexual interest were solely men but men are more likely to develop PD in almost a 2:1 ratio, therefore male predominance may not indicate an increases likelihood of hypersexual behaviors in males.

Table 7.14-Hypersexuality in Controlled Clinical Trials Pool V

I.D.	Age	Sex	Drug/Dose	AE Term	Outcome	Serious
(b) (6)	65	M	Istradefylline 40 mg/day	INCREASED SEXUAL AROUSAL	Ongoing	N
	60	M	Istradefylline 40 mg/day	HYPERSEXUALITY	Ongoing	N
	77	M	Istradefylline 20 mg/day	INCREASED SEXUAL URGE	Resolved	N

*Sexual dysfunction or decreased libido reported in two in the placebo group and two in the istradefylline treated group, there were no cases of increases libido or sexual interest reported in the placebo treated group discovered in the AE dataset.

Impulse Control Disorders Pool II (Long-term trials in Parkinson's)

Adverse events reported for increased sexual interest and compulsive gambling is numerically greater in Pool II but little can be said about rates, association with istradefylline or disease related factors. Comparisons with a control group are not possible in long-term trials and

the methods of eliciting information concerning ICDs, limits the usefulness of long-term trials data for determining an incident rate..

Table 7.15-Hypersexuality In Long-Term Trials (Pool II) No Control Group Available

I.D.	Age	Sex	Drug/Dose	AE Term	Outcome	Serious
(b) (6)	62	M	Istradefylline 40 mg/day	INCREASED LIBIDO	Ongoing	N
	66	M	Istradefylline 40 mg/day	INCREASED SEXUAL AROUSAL	Resolved	N
	60	M	Istradefylline 40 mg/day	HYPERSEXUALITY	Resolved	N
	60	M	Istradefylline 40 mg/day	HYPERSEXUALITY	Ongoing	N
	50	M	Istradefylline 40 mg/day	SEXUAL PREOCCUPATIONS	Resolved	N
	66	M	Istradefylline 40 mg/day	HYPERSEXUALITY	Resolved	N
	87	M	Istradefylline 40 mg/day	HYPER SEXUALITY	Resolved	N
	61	M	Istradefylline 40 mg/day	INCREASED SEXUAL THOUGHTS	Resolved	N
	62	M	Istradefylline 40 mg/day	HYPERSEXUALITY	Ongoing	N
	70	M	Istradefylline 40 mg/day	INCREASED SEXUAL DRIVE	Resolved	N
	70	M	Istradefylline 40 mg/day	HYPESEXUALITY	Resolved	N
	64	M	Istradefylline 40 mg/day	HYPERSEXUALITY	Resolved	N
	59	M	Istradefylline 40 mg/day	IMPULSIVE SEXUAL BEHAVIORS	Ongoing	N
	83	M	Istradefylline 60 mg/day	INCREASED SEXUAL PREOCCUPATION	Resolved	N

Table 7.16-Patholgical Gambling In Long-Term Trials (Pool II)

I D	Age	Sex	Drug/Dose	AE TERM	Outcome	Serious
(b) (6)	68	F	Istradefylline 40 mg/day	OBSESSIVE GAMBLING	Resolved	N
	43	M	Istradefylline 40 mg/day	INCREASED DESIRE TO GAMBLE	Resolved	N
	48	M	Istradefylline 40 mg/day	GAMBLING COMPULSION	Resolved	N
	61	M	Istradefylline 40 mg/day	GAMBLING	Ongoing	N
	65	M	Istradefylline 40 mg/day	EXCESSIVE GAMBLING	Resolved	N
	59	M	Istradefylline 40 mg/day	COMPULSIVE GAMBLING	Resolved	N
	75	M	Istradefylline 40 mg/day	PATHOLOGICAL GAMBLING	Resolved	Y
	70	M	Istradefylline 40 mg/day	COMPULSIVE GAMBLING	Resolved	N
	44	M	Istradefylline 60 mg/day	PROBLEMATIC GAMBLING	Ongoing	N

Reviewer Comment

Controlled clinical trial data suggest istradefylline is likely associated with an increased risk of for ICDs in patients with PD, compared to placebo. This is a significant finding since the mechanism of action of istradefylline is adenosine A2A receptor antagonism and it does not directly stimulate dopamine receptors. Istradefylline is also first in the class of A2A receptor antagonists to complete a program of clinical testing and this information may be helpful in planning future trials of istradefylline or other A2A receptor antagonists. If istradefylline gains agency approval Kyowa should be required to investigate the association of istradefylline with ICDs in PD patients, in a post-marketing commitment.

7.1.9 Less Common Adverse Events

There were no instances of "designated events" such as aplastic anemia, Steven's Johnson Syndrome, hepatic failure or acute renal failure arising in a subject without pre-existing renal disease.

LABORATORY FINDINGS

7.1.9.1 Overview of laboratory testing in the development program

Routine clinical labs were measured at the screening visit and every study visit (4 weeks apart) included CBC, chemistry, electrolytes and urinalysis. There were no laboratory abnormalities identified in early phases of clinical development or in animal studies that suggested the need to monitoring of clinical labs more frequently. The sponsor identified Possibly Clinically Significant (PCS) lab values for each parameter and they remained similar for each of the clinical trials included in this review. The PCS criteria were appropriately defined for both the direction and magnitude of change of each parameter. The sponsor defined PCS laboratory values that would raise concern in typical medical practice.

7.1.9.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The trial designs for the 5 pivotal studies were all, very similar. There were no laboratory investigations that were unique to a particular study. Data from Pool I incorporated all of the 5 pivotal trials and Pool II contained data from long-term safety studies. Therefore, this reviewer used pooled clinical laboratory data from in pool I as the primary data source to examine changes in central tendencies for clinical labs and compare them to the placebo groups. Individual studies were reviewed for outliers and unique clinical lab related safety events.

7.1.9.3 Standard analyses and explorations of laboratory data

7.1.9.3.1 Analyses focused on measures of central tendency

Pool I

Table 7.17-Kyowa Table Summary Statistics for Hematology Parameters in Pool I

Table 8.H-123 Summary Statistics by Laboratory Test: Hematology: Pool I

	Mean (range)									
	Baseline					Change from Baseline to Endpoint				
		Istradefylline/day					Istradefylline/day			
Analyte (unit)	Placebo N=561	10 mg N=153	20 mg N=427	40 mg N=440	60 mg N=155	Placebo N=561	10 mg N=153	20 mg N=427	40 mg N=440	60 mg N=155
Hemoglobin (g/L)	141.0 (101; 180)	141.3 (106; 171)	142.4 (90; 187)	142.6 (104; 182)	145.3 (106; 194)	-0.1 (-27; 23)	-0.9 (-19; 16)	-0.6 (-44; 25)	-1.1 (-64; 27)	-0.3 (-45; 19)
Hematocrit	0.427 (0.31; 0.53)	0.428 (0.34; 0.52)	0.428 (0.28; 0.56)	0.433 (0.33; 0.61)	0.430 (0.34; 0.56)	0.000 (-0.07; 0.07)	-0.002 (-0.07; 0.08)	-0.001 (-0.09; 0.10)	-0.002 (-0.20; 0.07)	-0.000 (-0.13; 0.05)
WBC ($x10^9$/L)	6.367 (2.76; 17.68)	6.139 (2.08; 11.05)	6.506 (3.13; 13.04)	6.354 (1.28; 13.84)	6.668 (3.52; 18.93)	0.150 (-6.70; 12.33)	0.040 (-3.21; 8.25)	0.003 (-5.19; 7.25)	0.042 (-6.22; 5.63)	-0.023 (-10.44; 4.05)
Platelets ($x10^9$/L)	245.2 (113; 548)	239.4 (121; 398)	247.4 (88; 737)	245.8 (64; 562)	237.0 (116; 409)	2.8 (-131; 236)	0.3 (-91; 117)	1.8 (-124; 266)	7.1 (-94; 140)	6.7 (-93; 255)
RBC ($x10^{12}$/L)	4.74 (3.3; 7.4)	4.80 (3.8; 6.3)	4.75 (3.1; 6.4)	4.78 (3.5; 7.2)	4.74 (3.8; 6.6)	0.02 (-0.7; 0.8)	-0.01 (-0.7; 0.6)	0.00 (-1.2; 0.9)	-0.01 (-1.9; 0.8)	-0.01 (-1.3; 0.5)
Abs. neutrophils/ polys ($x10^9$/L)	4.212 (1.64; 16.38)	4.065 (1.07; 8.59)	4.476 (0.85; 10.46)	4.228 (0.79; 11.30)	4.534 (1.92; 17.21)	0.134 (-7.72; 6.00)	0.037 (-3.18; 4.74)	0.017 (-4.69; 6.72)	0.079 (-6.01; 6.46)	0.005 (-11.29; 4.81)
Abs. lymphocytes ($x10^9$/L)	1.627 (0.46; 4.35)	1.559 (0.61; 3.38)	1.517 (0.42; 5.68)	1.589 (0.41; 3.86)	1.565 (0.63; 3.93)	0.018 (-1.45; 11.33)	0.000 (-1.03; 1.92)	-0.023 (-2.18; 0.90)	-0.032 (-2.05; 1.26)	-0.016 (-1.90; 1.43)
Abs. monocytes ($x10^9$/L)	0.342 (0.07; 1.20)	0.338 (0.11; 0.72)	0.342 (0.05; 1.14)	0.357 (0.04; 1.07)	0.364 (0.13; 0.98)	0.003 (-0.70; 1.40)	-0.011 (-0.40; 0.26)	0.005 (-0.56; 0.60)	-0.011 (-0.80; 0.45)	-0.008 (-0.45; 0.59)
Abs. eosinophils ($x10^9$/L)	0.142 (0.00; 1.20)	0.137 (0.00; 0.48)	0.126 (0.00; 0.60)	0.136 (0.00; 0.80)	0.149 (0.02; 0.48)	-0.004 (-0.61; 0.64)	0.007 (-0.24; 0.45)	0.003 (-0.51; 1.33)	0.002 (-0.40; 0.90)	-0.004 (-0.35; 0.35)
Abs. basophils ($x10^9$/L)	0.044 (0.00; 0.20)	0.039 (0.00; 0.14)	0.045 (0.00; 0.19)	0.045 (0.00; 0.23)	0.054 (0.00; 0.17)	-0.001 (-0.16; 0.23)	-0.005 (-0.09; 0.05)	0.000 (-0.15; 0.15)	0.001 (-0.18; 0.13)	0.000 (-0.17; 0.17)

Abs. = absolute, RBC = red blood count, WBC = white blood count
Source: Table S.2.3.1.1.1, Table S.2.3.1.2.1, Table S.2.3.1.3.1, Table S.2.3.1.4.1, Table S.2.3.1.5.1, Table S.2.3.1.6.1, Table S.2.3.1.7.1, Table S.2.3.1.8.1, Table S.2.3.1.9.1, Table S.2.3.1.10.1

Reviewer's Comment

There were no significant identified trends between the istradefylline treated groups and placebo for the mean change from baseline to endpoint for any hematology lab parameter in pool I.

Table 7.18-Kyowa Table Summary Statistics for Chemistry parameters in Pool I

Table 8.H-127 Summary Statistics by Laboratory Test: Blood Chemistry: Pool I

	Mean (range)									
	Baseline					Change from Baseline to Endpoint				
		Istradefylline/day					Istradefylline/day			
Analyte (unit)	Placebo N=561	10 mg N=153	20 mg N=427	40 mg N=440	60 mg N=155	Placebo N=561	10 mg N=153	20 mg N=427	40 mg N=440	60 mg N=155
SGPT (U/L)	18.2 (3; 163)	16.5 (4; 63)	17.6 (4; 61)	18.2 (4; 122)	19.8 (1; 52)	−1.0 (-125; 38)	0.3 (-20; 41)	0.8 (-27; 39)	0.2 (-85; 47)	1.7 (-23; 80)
SGOT (U/L)	21.0 (7; 281)	20.1 (11; 48)	20.5 (9; 46)	20.7 (8; 57)	21.0 (6; 45)	−0.9 (-257; 37)	0.7 (-14; 89)	0.4 (-20; 24)	0.3 (-41; 21)	1.4 (-17; 30)
Total bilirubin (mg/dL)	0.54 (0.2; 3.6)	0.51 (0.2; 2.6)	0.55 (0.2; 2.4)	0.58 (0.2; 2.5)	0.58 (0.2; 2.0)	0.01 (-0.8; 1.5)	0.01 (-0.7; 1.3)	0.02 (-0.8; 0.9)	0.04 (-1.0; 1.2)	0.02 (-0.7; 0.5)
Alkaline phosphatase (U/L)	84.2 (23; 483)	88.4 (40; 255)	83.1 (24; 304)	81.3 (34; 216)	75.7 (31; 144)	0.9 (-110; 307)	0.1 (-50; 97)	2.2 (-75; 138)	1.9 (-45; 102)	2.8 (-30; 66)
Lactate dehydrogenase (U/L)	173.5 (60; 324)	175.8 (70; 309)	170.0 (80; 292)	172.5 (99; 379)	165.9 (95; 270)	1.4 (-163; 142)	4.6 (-129; 417)	5.8 (-79; 92)	6.5 (-80; 1269)	9.1 (-79; 111)
Creatinine phosphokinase (U/L)	131.3 (18; 1274)	128.3 (36; 913)	121.6 (23; 1390)	120.6 (23; 1354)	127.9 (20; 613)	1.2 (-767; 1287)	−0.2 (-632; 641)	7.3 (-891; 988)	1.2 (-1282; 583)	13.3 (-212; 1432)
Sodium (mmol/L)	141.4 (130; 151)	141.0 (132; 148)	141.6 (132; 152)	141.3 (128; 155)	142.3 (136; 152)	−0.2 (-11; 30)	0.2 (-6; 7)	0.1 (-12; 35)	−0.2 (-12; 9)	−0.5 (-8; 8)
Potassium (mmol/L)	4.28 (3.0; 6.0)	4.23 (3.4; 5.7)	4.28 (3.2; 5.4)	4.29 (3.2; 6.3)	4.36 (3.2; 5.9)	0.01 (-1.1; 1.1)	-0.03 (-1.6; 1.1)	0.03 (-1.2; 1.6)	0.00 (-1.9; 1.0)	-0.02 (-1.0; 0.8)
Calcium (mg/dL)	9.60 (8.5; 11.1)	9.60 (8.7; 10.7)	9.64 (8.5; 11.9)	9.59 (8.1; 10.9)	9.64 (8.7; 11.6)	0.03 (-1.3; 1.0)	0.01 (-0.8; 0.9)	0.00 (-1.5; 1.2)	0.04 (-1.5; 1.3)	0.00 (-1.6; 1.2)
Chloride (mmol/L)	104.2 (94; 114)	103.6 (95; 110)	104.9 (94; 115)	104.2 (91; 116)	106.7 (96; 119)	0.0 (-8; 29)	0.3 (-5; 7)	0.2 (-10; 27)	−0.1 (-10; 11)	−0.1 (-6; 14)
Creatinine (mg/dL)	0.89 (0.4; 1.6)	0.89 (0.5; 1.6)	0.90 (0.4; 2.1)	0.90 (0.5; 4.3)	0.90 (0.5; 1.8)	0.01 (-0.6; 0.9)	0.01 (-0.3; 0.9)	0.00 (-0.4; 0.4)	0.00 (-3.6; 0.4)	0.00 (-0.5; 0.3)
[illegible]										
BUN (mg/dL)	18.8	19.4	19.2	18.5	19.2	0.2	0.6	0.5	−0.2	0.4
Trypsin-like immunoreactive (ng/mL)	44.03 (8.1; 376.8)	42.46 (15.2; 147.3)	44.06 (4.2; 324.3)	43.51 (4.0; 206.1)	44.52 (13.3; 156.5)	−1.07 (-359.7; 341.2)	1.69 (-111.1; 417.8)	0.94 (-174.2; 530.5)	−2.08 (-167.2; 135.5)	−0.28 (-52.2; 125.1)
Amylase (U/L)	63.2 (17; 191)	61.4 (25; 267)	63.5 (21; 218)	62.9 (13; 308)	58.1 (25; 133)	−0.6 (-126; 125)	−1.0 (-186; 52)	0.3 (-131; 149)	−1.6 (-207; 70)	−0.2 (-39; 45)
Lipase (U/L)	37.1 (12; 243)	35.4 (13; 105)	36.7 (13; 306)	37.0 (8; 320)	34.9 (16; 140)	-0.3 (-177; 277)	0.2 (-69; 120)	11.0 (-143; 256)	−1.9 (-287; 177)	-1.8 (-81; 20)
Glucose (mg/dL)	103.6 (42; 340)	102.9 (50; 283)	103.6 (61; 270)	105.0 (47; 389)	104.5 (57; 435)	−1.5 (-218; 188)	1.4 (-85; 101)	−1.7 (-140; 97)	−2.0 (-239; 204)	−0.8 (-279; 91)
Triglycerides (mg/dL)	145.2 (34; 1042)	154.9 (42; 494)	139.7 (27; 730)	140.7 (34; 568)	142.1 (35; 754)	−1.5 (-793; 307)	1.2 (-322; 201)	−3.8 (-304; 252)	−2.5 (-376; 311)	−7.0 (-537; 474)
Total cholesterol (mg/dL)	195.2 (109; 330)	188.9 (117; 325)	192.2 (94; 327)	195.7 (104; 317)	192.9 (129; 292)	−0.3 (-106; 107)	−0.4 (-111; 54)	−1.6 (-96; 88)	−2.2 (-133; 76)	0.5 (-103; 80)
Albumin [a] (g/L)	41.4 (33; 49)	41.6 (33; 48)	41.3 (21; 50)	41.7 (33; 50)	-	−0.1 (-15; 7)	−0.3 (-6; 5)	0.1 (-8; 9)	−0.2 (-12; 9)	-
Magnesium [a] (mg/dL)	2.10 (1.6; 2.7)	2.12 (1.4; 2.7)	2.14 (1.5; 3.5)	2.08 (1.7; 2.5)	-	−0.02 (-0.6; 0.5)	0.01 (-0.3; 0.4)	−0.01 (-1.2; 0.4)	−0.02 (-0.5; 0.4)	-
Uric acid [a] (mg/dL)	5.07 (1.8; 9.9)	5.03 (1.8; 8.6)	5.20 (2.1; 10.8)	4.97 (2.2; 9.7)	-	0.00 (-2.6; 2.7)	0.09 (-2.6; 3.6)	0.07 (-3.3; 4.9)	0.18 (-2.3; 4.7)	-

[a] These analytes were not measured in Studies 6002-US-005 and 6002-US-006.
BUN = blood urea nitrogen, SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic-pyruvic transaminase
Source: Table S.2.3.2.1.1, Table S.2.3.2.2.1, Table S.2.3.2.3B.1, Table S.2.3.2.4.1, Table S.2.3.2.5.1, Table S.2.3.2.6.1, Table S.2.3.2.7.1, Table S.2.3.2.8.1, Table S.2.3.2.9B.1, Table S.2.3.2.10.1, Table S.2.3.2.11B.1, Table S.2.3.2.12B.1, Table S.2.3.2.13.1, Table S.2.3.2.14.1, Table S.2.3.2.15.1, Table S.2.3.2.16B.1, Table S.2.3.2.17B.1, Table S.2.3.2.18B.1, Table S.2.3.2.19.1, Table S.2.3.2.20B.1, Table S.2.3.2.21B.1

Reviewer Comment

Analysis of the mean change from baseline to endpoint for the blood chemistry data did not find a significant difference between the placebo and istradefylline treated groups. There were no trends indicating a specific chemistry abnormality by dose.

Although hyperglycemia was one of the most commonly reported clinical lab abnormalities the mean serum glucose value by dose did not suggest this was a dose related adverse effect or that the mean glucose level was substantially greater in the istradefylline treated groups.

Table 7.18-Pool 1 Mean Glucose by Dose Baseline-Endpoint

Treatment group	Mean Glucose	Min Glucose	Max Glucose
Istradefylline 10 mg/day	103.45	49	283
Istradefylline 20 mg/day	102.09	45	357
Istradefylline 40 mg/day	104.01	44	435
Istradefylline 60 mg/day	103.22	57	435
Placebo	102.09	41	380

Table 7.19-Pool II Clinical Chemistry Data

Table 8.H-126 Summary Statistics by Laboratory Test: Blood Chemistry: Pool II: Continuous Exposure Method 1

	Mean (range)					
	Baseline			Change from Baseline to Endpoint		
	Istradefylline/day			Istradefylline/day		
Analyte (unit)	40 mg (N=1184)	60 mg (N=284)	Total (N=1468)	40 mg (N=1184)	60 mg (N=284)	Total (N=1468)
SGPT (U/L)	17.3 (1; 74)	21.2 (3; 93)	18.1 (1; 93)	−1.6 (−49; 452)	−5.0 (−62; 101)	−2.2 (−62; 452)
SGOT (U/L)	20.6 (6; 63)	21.2 (9; 48)	20.7 (6; 63)	0.3 (−42; 539)	−0.7 (−27; 50)	0.1 (−42; 539)
Total bilirubin (mg/dL)	0.58 (0.2; 3.2)	0.55 (0.2; 1.7)	0.58 (0.2; 3.2)	-0.03 (−2.1; 1.2)	−0.03 (−0.7; 2.4)	−0.03 (−2.1; 2.4)
Alkaline phosphatase (U/L)	83.8 (27; 478)	79.8 (37; 300)	83.0 (27; 478)	0.7 (−232; 118)	0.6 −120; 169)	0.6 (−232; 169)
Lactate dehydrogenase (U/L)	176.2 (69; 397)	166.9 (55; 338)	174.4 (55; 397)	3.4 (130; 1326)	−0.1 (−113; 145)	2.7 (−130; 1326)
Creatinine phosphokinase (U/L)	129.7 (18; 1771)	124.9 (25; 1497)	128.8 (18; 1771)	−1.2 (−1135; 3574)	−6.7 (−1436; 374)	−2.3 (−1436; 3574)
Sodium (mmol/L)	141.0 (128; 159)	142.6 (134; 180)	141.3 (128; 180)	−0.1 (−21; 13)	−0.8 (−32; 11)	−0.2 (−32; 13)
Potassium (mmol/L)	4.27 (2.5; 6.0)	4.37 (2.9; 6.0)	4.29 (2.5; 6.0)	0.00 (−1.4; 1.6)	−0.05 (−1.6; 1.1)	−0.01 (−1.6; 1.6)
Calcium (mg/dL)	9.61 (8.1; 11.3)	9.67 (8.5; 11.0)	9.62 (8.1; 11.3)	0.01 (−1.9; 1.3)	−0.08 (−1.1; 1.3)	−0.01 (−1.9; 1.3)
Chloride (mmol/L)	104.1 (91; 125)	107.1 (95; 138)	104.7 (91; 138)	0.0 (−22; 11)	−0.2 (−32; 13)	0.0 (−32; 13)
Creatinine (mg/dL)	0.90 (0.4; 2.1)	0.90 (0.4; 2.0)	0.90 (0.4; 2.1)	0.02 (−0.7; 1.0)	−0.02 (−0.5; 0.5)	0.01 (−0.7; 1.0)
BUN (mg/dL)	19.0 (6; 44)	19.4 (8; 48)	19.1 (6; 48)	0.6 (−19; 23)	0.4 (−12; 26)	0.5 (−19; 26)
Trypsin-like immunoreactive (ng/mL)	41.72 (4.0; 565.5)	45.55 (7.4; 436.5)	42.48 (4.0; 565.5)	−2.12 (−530.0; 562.6)	−1.07 (−319.7; 177.4)	−1.91 (−530.0; 562.6)
Amylase (U/L)	62.9 (15; 452)	60.8 (23; 213)	62.5 (15; 452)	−0.3 (−265; 138)	1.6 (−123; 106)	0.1 (−265; 138)
Lipase (U/L)	36.7 (9; 636)	35.3 (12; 275)	36.4 (9; 636)	−0.8 (−599; 253)	0.1 (-227;216)	−0.6 (−599; 253)
Glucose (mg/dL)	102.2 (29; 357)	101.3 (55; 364)	102.0 (29; 364)	0.2 (−175; 200)	−0.9 (−260; 139)	0.0 (−260; 200)
Triglycerides (mg/dL)	141.0 (33; 654)	131.4 (33; 629)	139.1 (33; 654)	1.2 (−343; 544)	8.3 (−264; 338)	2.6 (−343; 544)
Total cholesterol (mg/dL)	193.1 (73; 320)	192.7 (117; 284)	193.0 (73; 320)	−3.9 (−141; 102)	−6.5 (−103; 71)	−4.4 (−141; 102)

Table continued on next page

Reviewer Comment

Analysis of the laboratory data in Pool II did not find that istradefylline was associated with a significant change from baseline to endpoint in the mean chemistry values..

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.20-Pool I Shift Tables Hematology

Table 8.H-125 Shift Table Results by Laboratory Test: Hematology: Pool I

	Number of Subjects (%)[a]									
	With Decrease from Normal to Low					With Increase from Normal to High				
		Istradefylline/day					Istradefylline/day			
Analyte (unit)	Placebo N=561	10 mg N=153	20 mg N=427	40 mg N=440	60 mg N=155	Placebo N=561	10 mg N=153	20 mg N=427	40 mg N=440	60 mg N=155
Hemoglobin (g/L)	39 (7.0)	6 (3.9)	22 (5.2)	24 (5.5)	4 (2.6)	5 (0.9)	2 (1.3)	5 (1.2)	7 (1.6)	3 (1.9)
Hematocrit	21 (3.8)	3 (2.0)	16 (3.8)	16 (3.7)	3 (1.9)	14 (2.5)	2 (1.3)	7 (1.6)	7 (1.6)	5 (3.2)
WBC ($x10^9$/L)	29 (5.2)	8 (5.3)	16 (3.8)	24 (5.5)	2 (1.3)	23 (4.1)	3 (2.0)	13 (3.1)	19 (4.3)	4 (2.6)
Platelet ($x10^9$/L)	4 (0.7)	1 (0.7)	2 (0.5)	1 (0.2)	4 (2.6)	23 (4.1)	1 (0.7)	13 (3.1)	15 (3.4)	3 (1.9)
RBC ($x10^{12}$/L)	39 (7.0)	3 (2.0)	31 (7.3)	25 (5.7)	9 (5.8)	5 (0.9)	2 (1.3)	2 (0.5)	2 (0.5)	1 (0.6)
Abs. neutrophils/ polys ($x10^9$/L)	17 (3.1)	2 (1.3)	10 (2.3)	10 (2.3)	2 (1.3)	49 (8.8)	6 (3.9)	23 (5.4)	35 (8.0)	7 (4.5)
Abs. lymphocytes ($x10^9$/L)	33 (5.9)	9 (5.9)	28 (6.6)	27 (6.2)	7 (4.5)	13 (2.3)	3 (2.0)	3 (0.7)	4 (0.9)	2 (1.3)
Abs. monocytes ($x10^9$/L)	19 (3.4)	3 (2.0)	13 (3.1)	16 (3.7)	1 (0.6)	5 (0.9)	0	3 (0.7)	4 (0.9)	1 (0.6)
Abs eosinophils ($x10^9$/L)	0	0	0	0	0	14 (2.5)	1 (0.7)	6 (1.4)	10 (2.3)	4 (2.6)
Abs basophils ($x10^9$/L)	0	0	0	0	0	6 (1.1)	0	2 (0.5)	1 (0.2)	1 (0.6)

[a] Percentages are based on the number of subjects with data at Baseline and post-Baseline within each analyte.
Abs. = absolute, RBC = red blood count, WBC = white blood count
Source: Table S.2.3.4.1

Reviewer Comment

There were no significant shifts from normal to abnormal in hematological parameters for istradefylline compared to placebo in pool I. There were trends following a dose related numerical increase but there were no specific dose-dependent changes in hematology lab values.

Table 7.21- Kyowa Shift Tables for Chemistry Lab Results Pool I.

Table 8.H-127 Shift Table Results by Laboratory Test: Blood Chemistry: Pool I

	Number of Subjects (%)[a]									
	With Decrease from Normal to Low					With Increase from Normal to High				
		Istradefylline/day					Istradefylline/day			
Analyte (unit)	Placebo (N=561)	10 mg (N=153)	20 mg (N=427)	40 mg (N=440)	60 mg (N=155)	Placebo (N=561)	10 mg (N=153)	20 mg (N=427)	40 mg (N=440)	60 mg (N=155)
SGPT (U/L)	33 (5.9)	9 (5.9)	29 (6.8)	24 (5.5)	5 (3.2)	33 (5.9)	8 (5.2)	21 (4.9)	37 (8.4)	16 (10.4)
SGOT (U/L)	14 (2.5)	2 (1.3)	6 (1.4)	7 (1.6)	0	28 (5.0)	9 (5.9)	17 (4.0)	41 (9.4)	21 (13.6)
Total bilirubin (µmol/L)	14 (2.5)	6 (3.9)	6 (1.4)	10 (2.3)	2 (1.3)	24 (4.3)	4 (2.6)	15 (3.5)	28 (6.4)	10 (6.5)
Alkaline phosphatase (U/L)	0	0	0	1 (0.2)	1 (0.6)	27 (4.8)	11 (7.2)	23 (5.4)	26 (5.9)	7 (4.5)
LDH (U/L)	0	0	0	0	0	37 (6.6)	12 (7.8)	37 (8.7)	45 (10.3)	16 (10.4)
Creatinine phosphokinase (U/L)	1 (0.2)	0	0	0	0	105 (18.8)	31 (20.3)	96 (22.5)	95 (21.7)	28 (18.2)
Sodium (mmol/L)	13 (2.3)	3 (2.0)	3 (0.7)	12 (2.7)	2 (1.3)	49 (8.8)	9 (5.9)	41 (9.6)	44 (10.0)	16 (10.4)
Potassium (mmol/L)	8 (1.4)	1 (0.7)	8 (1.9)	5 (1.1)	1 (0.6)	5 (0.9)	0	6 (1.4)	5 (1.1)	3 (1.9)
Calcium (mmol/L)	8 (1.4)	0	2 (0.5)	6 (1.4)	2 (1.3)	12 (2.1)	4 (2.6)	11 (2.6)	9 (2.1)	10 (6.5)
Chloride (mmol/L)	4 (0.7)	0	0	3 (0.7)	0	13 (2.3)	2 (1.3)	13 (3.0)	5 (1.1)	3 (1.9)
Creatinine (µmol/L)	1 (0.2)	0	1 (0.2)	1 (0.2)	0	14 (2.5)	9 (5.9)	12 (2.8)	9 (2.1)	8 (5.2)
BUN (mmol/L)	0	0	0	0	0	73 (13.1)	22 (14.4)	73 (17.1)	51 (11.6)	24 (15.6)
Trypsin-like immunoreactive (ng/mL)	36 (6.5)	10 (6.5)	21 (4.9)	20 (4.6)	7 (4.5)	20 (3.6)	3 (2.0)	13 (3.1)	8 (1.8)	3 (1.9)
Amylase (U/L)	17 (3.0)	5 (3.3)	19 (4.4)	15 (3.4)	0	20 (3.6)	2 (1.3)	18 (4.2)	15 (3.4)	14 (9.1)
Lipase (U/L)	0	0	0	0	0	36 (6.4)	2 (1.3)	35 (8.2)	21 (4.8)	9 (5.8)
Glucose (mmol/L)	41 (7.3)	4 (2.6)	22 (5.2)	26 (5.9)	8 (5.2)	97 (17.4)	31 (20.3)	83 (19.4)	86 (19.6)	40 (26.0)
Triglycerides (mmol/L)	52 (9.3)	10 (6.5)	43 (10.1)	34 (7.8)	13 (8.4)	57 (10.2)	17 (11.1)	35 (8.2)	44 (10.0)	11 (7.1)

Table continued on next page

Reviewer Comment

There is a dose related increase in the percentage of subjects with AST or ALT shifts from normal to abnormally high in the istradefylline treated groups. The difference in the number of subjects who shifted is most pronounced above 20 mg/day. Despite shift table findings, there were no cases of hepatic failure reported during the trial and the reviewer's analysis did not find case of treatment emergent increases in AST or ALT associated with an increase in bilirubin of > 1.5 X ULN. There were no individual subject reports meeting criteria for Hy's law cases. There were no other findings discovered in reviewing the results of the shift tables for changes in chemistry or hematology lab data comparing istradefylline to placebo.

Table 7.22-Pool II Shift Tables for Hematology Clinical Lab Values (Kyowa Table)

Table 8.H-124 Shift Table Results by Laboratory Test: Hematology: Pool II: Continuous Exposure Method 1

	Number of Subjects (%)[a]					
	With Decrease from Normal to Low			With Increase from Normal to High		
	Istradefylline/day			Istradefylline/day		
Analyte (unit)	40 mg (N=1184)	60 mg (N=284)	Total (N=1468)	40 mg (N=1184)	60 mg (N=284)	Total (N=1468)
Hemoglobin (g/L)	113 (9.9)	18 (6.6)	131 (9.3)	11 (1.0)	4 (1.5)	15 (1.1)
Hematocrit	59 (5.2)	25 (9.1)	84 (6.0)	31 (2.7)	2 (0.7)	33 (2.3)
WBC ($x10^9$/L)	68 (6.0)	7 (2.6)	75 (5.3)	90 (7.9)	25 (9.1)	115 (8.2)
Platelet ($x10^9$/L)	16 (1.4)	2 (0.7)	18 (1.3)	71 (6.3)	14 (5.1)	85 (6.1)
RBC ($x10^{12}$/L)	89 (7.8)	34 (12.4)	123 (8.7)	16 (1.4)	1 (0.4)	17 (1.2)
Abs. neutrophils/ polys ($x10^9$/L)	34 (3.0)	3 (1.1)	37 (2.6)	150 (13.2)	30 (10.9)	180 (12.8)
Abs. lymphocytes ($x10^9$/L)	74 (6.5)	12 (4.4)	86 (6.1)	29 (2.6)	10 (3.6)	39 (2.8)
Abs. monocytes ($x10^9$/L)	35 (3.1)	4 (1.5)	39 (2.8)	22 (1.9)	1 (0.4)	23 (1.6)
Abs. eosinophils ($x10^9$/L)	0	0	0	34 (3.0)	3 (1.1)	37 (2.6)
Abs. basophils ($x10^9$/L)	0	0	0	13 (1.1)	5 (1.8)	18 (1.3)

[a] Percentages are based on the number of subjects with data at Baseline and post-Baseline within each analyte.
WBC = white blood count, RBC = red blood count, Abs. = absolute
Source: Table S.2.3.4.2.1

Table 7.23 Serum Chemistry Shift Table for Lab Values (Kyowa Table)

Table 8.H-128 Shift Table Results by Laboratory Test: Blood Chemistry: Pool II: Continuous Exposure Method 1

	Number of Subjects (%)[a]					
	With Decrease from Normal to Low			With Increase from Normal to High		
	Istradefylline/day			Istradefylline/day		
Analyte (unit)	40 mg (N=1184)	60 mg (N=284)	Total (N=1468)	40 mg (N=1184)	60 mg (N=284)	Total (N=1468)
SGPT (U/L)	108 (9.4)	21 (7.4)	129 (9.0)	98 (8.5)	18 (6.4)	116 (8.1)
SGOT (U/L)	32 (2.8)	7 (2.5)	39 (2.7)	108 (9.4)	22 (7.9)	130 (9.1)
Total bilirubin (µmol/L)	36 (3.1)	8 (2.8)	44 (3.1)	60 (5.2)	11 (3.9)	71 (4.9)
Alkaline phosphatase (U/L)	0	1 (0.4)	1 (0.1)	92 (7.9)	8 (2.8)	100 (6.9)
Lactate dehydrogenase (U/L)	0	0	0	154 (13.6)	16 (5.8)	170 (12.1)
Creatine phosphokinase (U/L)	2 (0.2)	0	2 (0.1)	293 (25.3)	48 (17.0)	341 (23.7)
Sodium (mmol/L)	28 (2.4)	2 (0.7)	30 (2.1)	143 (12.3)	44 (15.6)	187 (13.0)
Potassium (mmol/L)	24 (2.1)	5 (1.8)	29 (2.0)	37 (3.2)	5 (1.8)	42 (2.9)
Calcium (mmol/L)	9 (0.8)	0	9 (0.6)	44 (3.8)	15 (5.3)	59 (4.1)
Chloride (mmol/L)	11 (0.9)	1 (0.4)	12 (0.8)	11 (0.9)	25 (8.9)	36 (2.5)
Creatinine (µmol/L)	1 (0.1)	0	1 (0.1)	59 (5.1)	6 (2.1)	65 (4.5)
BUN (mmol/L)	0	0	0	227 (19.6)	42 (14.8)	269 (18.6)
Trypsin-like immunoreactive (ng/mL)	94 (8.5)	18 (6.5)	112 (8.1)	36 (3.2)	8 (2.9)	44 (3.2)
Amylase (U/L)	79 (6.8)	0	79 (5.5)	55 (4.7)	24 (8.5)	79 (5.5)
Lipase (U/L)	0	0	0	76 (6.6)	26 (9.2)	102 (7.1)
Glucose (mmol/L)	100 (8.7)	16 (5.7)	116 (8.1)	353 (30.5)	66 (23.3)	419 (29.1)
Triglycerides (mmol/L)	131 (11.3)	25 (8.8)	156 (10.8)	152 (13.1)	31 (11.0)	183 (12.7)
Total cholesterol (mmol/L)	273 (23.5)	75 (26.5)	348 (24.1)	18 (1.6)	2 (0.7)	20 (1.4)

[a] Percentages are based on the number of subjects with data at Baseline and post-Baseline within each analyte.
Source: Table S.2.3.5.2.1

Reviewer Comment

The shift table results did not reveal a significant change, in the percent of subjects shifted to abnormal values for hematology or blood chemistry parameters.

Urinanalysis

There were no clinically significant differences in mean values for specific gravity pH, ketones, glucose, bilirubin nitrates, blood protein, urobilinogen, or color in Pool I or Pool II. Overall 10% of subjects included in pool 1 experienced a shift from normal to high in at least one of the urinanalysis parameters, but there were no significant differences between the istradefylline treated groups verses placebo.

7.1.9.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.10 Subject With Laboratory Adverse Events-Data from Single Studies

7.1.10.1 6002-US-005 Study

Clinical Lab Values

Hematology

There were no significant differences for changes in the mean values of hematological or chemistry lab values comparing baseline to endpoint or baseline to individual study visit. There were 5 cases of neutropenia that were < 3.9 WBC x 10^9 /L, in all 5 cases there baseline and screening visit values were also low. In all but one case the WBC remained stable through the course of the trial. In the subject were the WBC decreased (1.25 to 0.84 x 10^9 /L) the values were stable until week 12 (the final visit), given the low WBC of 1.25 x 10^9 /L at the screening visit this subject should have been excluded from trial participation. There were no cases of treatment emergent neutropenia, aplastic anemia or serious thrombocytopenia reported during the trial.

Alkaline Phosphatase

Four subjects who received istradefylline 40 mg/day had elevated alkaline phosphatase levels during the course of the trial. One subject had elevated levels at baseline but in all 4 subjects the levels remained higher than baseline over the course of the trial. In 2 subjects the elevation in alkaline phosphatase was accompanied by mild elevations of ALT and/or AST. One subject has a mildly elevated LDH as an isolated event in week 12 (endpoint).

Liver Enzymes

There were no subjects who met criteria for Hy's Law (ALT or AST ≥ 3 X ULN with total bilirubin ≥ 1.5 X ULN). There was only a single individual who had liver enzymes (ALT) approaching 3 X ULN measured at the baseline and week 8 visits. The AST and ALT were both mildly elevated at the baseline visit, the ALT increased greater than the AST that remained at a mildly elevated level (1.3 X ULN). There were no cases of hepatic failure reported during the trial. Mean changes in ALT and AST by study visit or form baseline did not indicate increasing liver enzymes.

Amylase and Lipase

The percent of subjects who experienced an increase in amylase or lipase was greater in the placebo group. A subject ((b) (6)) receiving 40 mg istradefylline/day experience a sudden elevation of amylase, lipase and trypsin-like immunoreactivity just prior to his unattended death. The cause of death was not attributed to pancreatitis but it cannot be excluded as a contributing factor. The mean group and individual subject change values for lipase, amylase and trypsin like immunoreactivity did not indicate increasing values over the course of the trial.

Chemistry and Glucose

Glucose, BUN and Triglycerides were the most frequently encountered abnormal lab values. Hypoglycemia (glucose < 3.0 mmol/L occurred in 4 subjects all receiving istradefylline 40 mg/day all instances were isolated events. Increases in glucose that occurred while on study medication were 3 in the placebo group and 1 in the istradefylline group. Increases in BUN occurred in 7.8% of the istradefylline treated group and 10 % of the placebo group. None of the increases in BUN were accompanied by a concomitant increase in creatinine. There were no instances of renal failure or clinically significant electrolyte derangement reported during the trial. Mean group change values and individual subject change values for BUN and creatinine did not suggest declining renal function.

7.1.10.2 6002-US-006 Study

Hepatic Enzymes

Subject (b) (6) (increased ALT, AST, LDH, CPK, aldolase, and total bilirubin)

44-year-old Caucasian male subject diagnosed with PD, was randomized to receive istradefylline 60mg/day. On Day 56, the subject experienced increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood lactate dehydrogenase (LDH), increased blood creatine phosphokinase (CPK), and increased aldolase. On Day 58, he experienced increased blood total bilirubin. The subject was withdrawn from treatment on day 58. A summary of the laboratory values is provided below:

Table 7.24-Study 6002-US-006 Subjects With Elevated Hepatic Enzymes (Kyowa Table)

Lab Parameter	Normal Range	Day -1 16 Oct	Week 2 28 Oct	Week 4 7 Nov	Week 8 11 Dec	Week 12[a] 13 Dec	Unsch 16 Dec	Unsch 18 Dec	Unsch 3 Jan
ALT	6-43 U/L	41	38	44 H	69 H	38	45 H	47 H	18
AST	11-36 U/L	33	33	42 H	152 HA	96 H	37 H	27 H	20
LDH	53-234 U/L	136	145	150	322 H	166	127	135	112
CPK	18-198 U/L	194	177	464 H	5892 H	1699 H	232 H	135	83
Aldolase	3-21µmol/L	6.8	5.4	9.7 H	106.6 H	--	12.9 H	8.2 H	3.7
Total Bilirubin	1.2-7.6 U/L	22 H	15	15	17	22 H	21	14	15

[a] Early discontinuation.
A = Potentially clinically significant (see Preface B); H = above the upper limits of the normal range; Unsch = unscheduled visit.
Note: Potentially clinically significant criteria were not established for CPK and aldolase.

The Investigator assessed all of these events as mild in intensity and not related to study drug. The increased LDH was considered to be resolved on Day 58; increased bilirubin was considered to be resolved on Day 61; increased AST and CPK were considered to be resolved on Day 63; and increased aldolase and ALT were considered to be resolved on day 63.

Reviewer Comment

The subjects AST, ALT and CPK were near the ULN at the baseline visit and the total bilirubin was approximately 3 X ULN at baseline. The subject should lot have been permitted to enter the trial based on the elevated bilirubin. The abnormal AST and ALT may be a result of worsening hepatobilary obstructive disease or caused by rhabdomyolysis. The reason for the elevation in CPK and aldolase is not mentioned in the sponsor's narrative. The temporal association of istradefylline to the increase in hepatic transaminases and CPK and resolution after withdrawal form suggests istradefylline may be associated to either potential cause of liver function test abnormalities..

Acute Renal Failure

Subject (b) (6)

A 78-year-old Caucasian male subject diagnosed with PD, had a significant medical history of arrhythmia, diverticulitis, Stage II chronic kidney disease, hematuria, left and right knee joint replacement, gout, hypercholesterolemia, and arthritis. The subject received istradefylline 60 mg/day. On Day 14, the subject experienced acute renal failure. The subject was withdrawn from treatment on Day 22. Concomitant medications at the time of the AE included atenolol 50 mg (arrhythmias), selegiline 5-10 mg (PD), tocopherol 400 IU (general health), allopurinol 300 mg (gout), gemfibrozil 600 mg (hypercholesterolemia), valdecoxib 10 mg (arthritis), and pergolide 0.75 mg (PD). The event was considered resolved on Day 28.

Table 7.25-Subject (b) (6) Summary of Laboratory Values (Kyowa Table)

Lab Parameter	Normal Range	Day -1 17 Jun	Week 2 1 Jul	Unscheduled 7 Jul	Unscheduled 9 Jul	Week 12[a] 15 Jul
BUN	1.4-10.4 mmol/L	12.1 HA	14.6 HA	20.3 HA	17.5 HA	11.8 HA
Creatinine	40-137 µmol/L	133	150 H	203 HA	186 HA	124
Sodium	135-145 mmol/L	139	138	139	136	140
Potassium	3.4-5.4 mmol/L	5.9 HA	--	5.9 HA	5.8 HA	5.4
Phosphate	2.9-5.7 U/L	3.7	4.1	--	2.8 L	1.7 L

[a] Early discontinuation
A = Potentially clinically significant (see Preface B); H = above the upper limits of the normal range;
L = below the lower limits of the normal range

Reviewer Comment

This subject had a history of mild pre-existing renal insufficiency prior to enrollment but there is no recommended istradefylline dose reduction in subjects with renal impairment. The subject had a clear worsening of renal function after starting istradefylline 60 mg/day, which improved with medication withdrawal. The possible cause for adverse event may be associated with a drug-drug interaction involving istradefylline or drug-disease interaction since the cause for the subjects renal insufficiency was not included in the sponsor's narrative.

7.1.10.3 6002-US-013 Study

Elevated Lipase

Subject (b) (6)

A 71 year-old Caucasian female with a significant medical history that included Parkinson's disease, constipation, acid reflux, lipase increased, neck, and elbow pain, poor sleeping pattern, and osteoporosis was randomized to istradefylline 20 mg. On Day 28 of the study, the subject experienced lipase increase (verbatim = increased lipase intermittent) (lipase = 422 U/L (normal 0-130 U/L); amylase = 145 U/L (Normal= 50-252); trypsin = 230.1 (normal 22.5-132.5) ng/mL) and withdrew from the study on Day 65. Follow reports from the site investigator indicated the AE was resolving.

7.1.10.4 6002-US-018 Study

Elevated Lipase

One subject in the placebo group, 3 subject to the istradefylline 20 mg and 1 in the istradefylline 40 mg group developed a treatment emergent elevation in serum lipase. Subject (b) (6) and (b) (6) had concomitant elevation of trypsin-like immunoreactivity suggesting pancreatitis. Subject (b) (6) was withdrawn from study medication on day 18, for pancreatitis

when the lab data became known to the investigator. The sponsor's narrative for this adverse event did not describe the subject as having clinical signs of pancreatitis.

Elevated Liver Function Tests

Two subjects were withdrawn from the study because of a TEAL relating to elevated liver enzymes. The first ((b) (6)) was withdrawn from istradefylline 20 mg/day on day 57 of the study because of an ALT of 109 U/L (32 U/L=ULN), AST of 85 U/L (34 U/L=ULN) and Alkaline Phosphatase of 519 U/L (123 U/L=ULN). On day 68 the subject was hospitalized for 2 days. Study medication was withdraw, the subject was also taking 9 concomitant medications, including atorvastatin, known to inhibit CYP3A4 and increase the exposure to istradefylline but regarded as safe for co-administration with istradefylline at a dose of 20 mg/day. Subject (b) (6) was discontinued from the study because of "hepatic enzymes increased". The abnormal hepatic enzymes were abnormally elevated at baseline ALT= 42 U/L (34 U/L=ULN) on study day 15 and the subject was withdrawn for the study because of elevations in the ALT and AST to > 3X ULN (ALT=130 U/L). Both TEALs were said to be resolved in the sponsor's narrative.

Subject 6002-US-018-(b) (6)

The subject was discontinued from the US-018 trial at week 2 because of elevation of AST > 3 X ULN (34 U/L). The subject's baseline value was elevated above the ULN at 46 U/L. The subject received 20 mg of istradefylline and on week 2 the AST had risen to 130 U/L. The subject's AST returned to the normal range 32 U/L after study medication was discontinued.

7.1.10.5 6002-EU-007 Study

Hepatic Enzymes

Subject (b) (6)

The subject withdrew from the study for an adverse event listed as "hepatic enzymes increased". He was randomized to the istradefylline 40 mg/day group and on day 42 he was discovered to have elevated hepatic enzymes. His ALT was > 8 X ULN with a AST > 5 X ULN at the week 6 study visit. The subject was discontinued from the study on day 72 and his hepatic enzymes were returning to but not back to baseline at the conclusion of the study (week 16). The subject's alkaline phosphatase and total bilirubin remained with in the normal range.

Subject (b) (6)

This subject had an elevated ALT and AST had an isolated elevation of AST and ALT discovered at the week 8 scheduled visit. The results of the AST and ALT measured at an unscheduled visit at study day 60 found there were returning towards the normal range. The subject's transaminases returned to the normal range by week 12 and remained with in the

normal range through out the conclusion of the trial (week 16). The subject's alkaline phosphatase and total bilirubin remained with in the normal range.

Subject (b) (6).

The subject was discontinued from study medication on study day 37 because of an unrelated TEAE, hallucination. His AST was greater the 3 X ULN with a elevated ALT that was approximately 2 X ULN. Both the AST and ALT returned to the normal range by day 58 and the alkaline phosphatase and total bilirubin remained with in the normal range.

Leukopenia/Neutropenia

Subject No. (b) (6)

The subject developed mild leukopenia at week 8 while on istradefylline The lowest WBC value was 3.34 X 10^9/L which occurred at week 16 (final visit). Follow up information was not included in the sponsor's narrative.

Reviewer Comment

Individual subject changes did not reveal new evidence suggesting rare severe adverse events. The individual lab related events developed over a period of several weeks and the majority of cases the events resolved by discontinuing istradefylline. In some of the individual cases of lab abnormalities the final outcome is not known.

7.2 Vital Signs

7.2.1.1 Overview of vital signs testing in the development program

Vital signs were monitored in a routine fashion in all of the pivotal clinical trials. The 6002-US-006 study monitored subjects with PD specifically for orthostatic changes in pulse and BP. The 6002-US-009 study monitored healthy volunteers for orthostatic changes in BP and pulse. The assessment of the potential association of istradefylline with hypotension or orthostatic hypotension was adequate.

7.2.2 Selection of studies and analyses for overall drug-control comparisons

Data from pool 1 from controlled clinic trials was the examined for changes in measures of central tendencies. The 6002-US-006 study was selected for review because the study was the only controlled trial that specifically monitored for orthostatic changes in vital signs in subjects relevant to the indication.

7.2.3 Standard analyses and explorations of vital signs data

7.2.3.1 Study 6002-US-009 Orthostatic Changes in Vital Signs in Healthy Volunteers

Kyowa conducted this 14-day, pK study to examine the effects of carbidopa/levodopa on the pK, safety parameters and orthostatic vital signs in 24 healthy volunteers' receiving istradefylline 80 mg/day. Subjects received istradefylline 80 mg/day for 14-days and carbidopa/levodopa 2-25/100 mg tablets on days 1 and 15. Vital signs were measured at baseline and included sitting systolic and diastolic blood pressure and 30-second brachial pulse rate measurements, were obtained at screening, Day -1, Days 1, 2, 8, 15, 16, at the final visit (Day 28), and as clinically indicated. On Days 1, 2 and 15, vital signs were measured pre-dose and at 2.0, 4.0, and 6.0 hours after dosing.

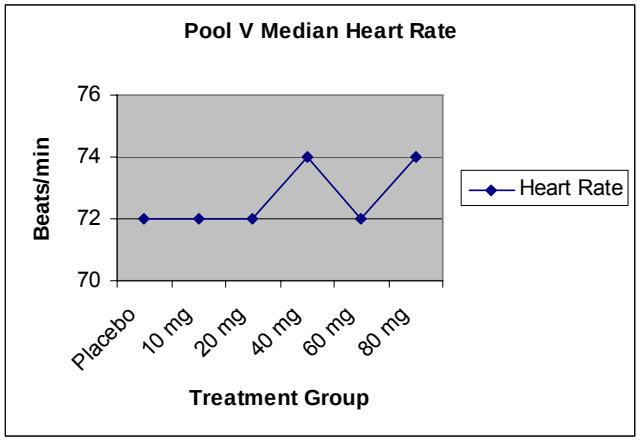
Orthostatic blood pressure and pulse rate measurements were obtained at screening, on Days 1, 2, and 15 pre-dose, and at 0.25 and 0.50 hours after dosing. The orthostatic vital sign measurements were timed to the Tmax of levodopa (at 0.25 and 0.5 hours). Blood pressure and pulse rate were measured after the subject had been in the supine position for 3 minutes. Standing blood pressure and pulse rate were obtained after the subject had been standing for 2 minutes.

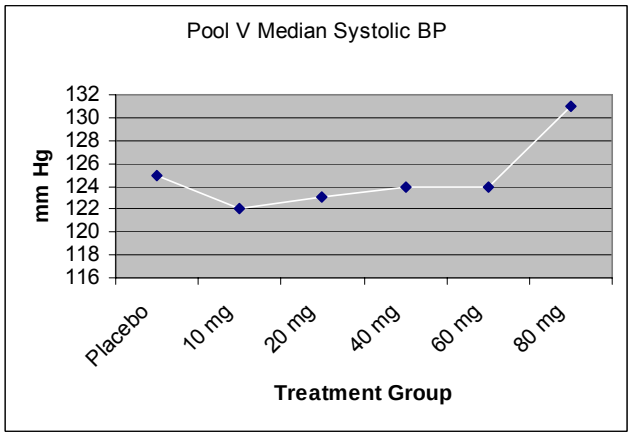
The criteria for orthostatic hypotension were as follows: decrease in systolic blood pressure ≥20 mm Hg; decrease in diastolic blood pressure ≥15 mm Hg; increase in pulse rate ≥20 bpm. Subject 024 met criteria for an isolated decrease in systolic blood pressure at 0.25 hours post-dose on Day 15, subject (b) (6) met criteria for an isolated decrease in diastolic blood pressure pre-dose on Day 15. Five subjects had isolated increases in pulse rate after exposure to levodopa. The remaining five subjects (Subjects (b) (6)) had isolated, treatment-emergent increases in pulse rate after starting KW-6002 treatment on Day 2. The cases of treatment-emergent increased pulse rate without a decline in systolic or diastolic BP during KW-6002 exposure are of unknown clinical relevance.

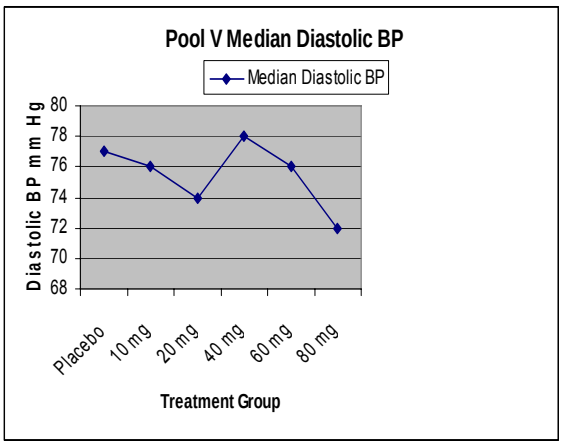
The data from this study did not suggest istradefylline 80 mg/day was associated with orthostatic changes in vital signs but the study was not timed to capture BP and pulse measurements at the Tmax of istradefylline (1-3 hours). The evaluation of subjects taking 80 mg of istradefylline daily and higher than average doses of levodopa is rational and mimics the use of both medications in patients with PD. There were no indications the combination of the two medications given together significantly increase the potential for orthostatic changes in vital signs in healthy volunteers.

7.2.3.1.1 Analyses focused on measures of central tendencies

Table 7.26-Reviewer's Analysis of Mean Heart Rate and BP by Dose of Istradefylline Pool V







Data on the 80 mg group is from the 6002-US-004 trial which enrolled a total of n=15 (3 placebo, n=12 istradefylline 80 mg/day in subjects with PD, for a duration of 8 weeks. The median BP at baseline was 132.5/74.5 for the istradefylline group and 132.0/84.0 in the placebo group. At week 8 the median BP for the istradefylline 80 mg group was 126/64 and 139/80 in the placebo treated group. There were no significant dose related changes in the mean BP or pulse in subjects participating in controlled clinical trials for all indications.

7.2.3.1.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.27-POOL I-Cohort With At Least 1 Episode Of A 15 mm Hg Decline In Systolic BP Compared To Baseline Value

Dose	N Exposed	N with at least 1 episode of ↓SYS BP ≤ 15 mm Hg compared to baseline	% with at least 1 episode of ↓ SYS BP decline of ≤15 mm Hg
Istradefylline 10 mg/day	155	50	32.26
Istradefylline 20 mg/day	428	154	35.98
Istradefylline 40 mg/day	441	171	38.78
Istradefylline 60 mg/day	155	68	43.87
Placebo	564	221	39.18

Reviewer Comment

There was no evidence for a significant change in pulse or BP based on the analysis of central tendencies performed by the sponsor or this reviewer. There were no significant or dose dependant between group differences in the percentage of subjects who experienced a 15 mm Hg decline in systolic BP compared to their Baseline visit as an isolated event.

7.2.3.1.3 Marked outliers and dropouts for vital sign abnormalities

Reviewer Comment

The only subject that received istradefylline and experienced a decline in systolic BP from supine to standing of -15 mg Hg or more was subject 6002-US-(b) (6). The maximum orthostatic decline in systolic BP was -30 mm Hg that was recorded at the Day (-8) visit. Outlier analysis of subjects with high systolic BP revealed 2 subjects with a systolic BP ≥ 180 mm Hg in the istradefylline 120 mg/day phase. In the first subject, elevated BP was an isolated event subject ((b) (6)) experienced the high systolic BP reading in the sitting position for a single reading. In the BP in the second subject ((b) (6)) with a single elevated systolic BP ≥ 180 mm Hg, had elevated systolic and diastolic BP recorded at all visits. During the placebo phase the same 2 subjects ((b) (6)) also had elevated systolic BP ≥ 180 mm Hg.

Two subjects discontinued study participation because of orthostatic hypotension (syncope) one in the placebo group and another who received istradefylline 20 mg/day. A second subject taking istradefylline had a history of syncope prior to his baseline visit experienced syncope and withdrew from the trial.

Study 6002-US-018

Orthostatic Hypotension

Two subjects experience syncope also termed orthostatic hypotension during the trial both event met criteria for reporting as an SAE. The first subject had a history of orthostatic hypotension that predated enrollment in the trial. The second subject had a single, self-limited episode of syncope on study day 57 while taking istradefylline 20 mg/day. He remained on study medication and on day 75 the subject fell and sustained a fracture of the acetabulum and ribs. He was hospitalized and a pulmonary embolism that required treatment complicated his recovery. There narrative did not mention if the subject's fall was caused by syncope.

7.2.3.2 Additional analyses and explorations

Table 7.28

Table 8.H-139 Study 6002-US-006: Summary of Subjects with Changes in Orthostatic Vital Sign Measurements That Met the Potentially Clinically Significant Criteria - (Safety Population)

Parameter	Placebo (N=77) n (%)	Istradefylline 20 mg/day (N=163) n (%)	Istradefylline 60 mg/day (N=155) n (%)
Subjects with any Orthostatic Vital Sign Values:	**47 (100)**	**106 (100)**	**109 (100)**
Subjects With Any PCS Orthostatic Changes[a] in Systolic Blood Pressure, Diastolic Blood Pressure and/or Pulse Rate:	17 (36.2)	51 (48.1)	45 (41.3)
Systolic Blood Pressure	8 (17.0)	31 (29.2)	22 (20.2)
Diastolic Blood Pressure	9 (19.1)	34 (32.1)	34 (31.2)
Pulse Rate	3 (6.4)	8 (7.5)	12 (11.0)

[a] Potentially significant criteria: systolic blood pressure: a decrease of ≥ 20 mm Hg from supine to standing position; diastolic blood pressure: a decrease of ≥ 10 mm Hg from supine to standing position; pulse rate: an increase of ≥ 20 bpm from supine to standing position.

Source: 6002-US-006 End-of-Text Table 14.3.10.4 and Listing 16.2.15.2

Table 7.29-Mean change in Systolic BP Supine to Standing in Study 6002-US-006 in Patients with PD

	Mean Sysolic BP mm Hg		Mean Diastolic BP mm Hg		Mean Change Stand-Supine mm Hg	
	Supine BP	Stand BP	Supine BP	Stand BP	Systolic	Diastolic
placebo	128.3	125.7	77.7	78.3	-2.6	0.6
20 mg	128.2	122.5	75.1	74.5	-5.7	-0.6
60 mg	128.7	125.7	76.2	75.4	-3	-0.8

Table 7.30-6002-US-006 Study Mean Orthostatic Change in Pulse

	Pulse		
	Supine	Stand	ΔSupine-Stand
Placebo	71.3	74.7	3.4
20 mg	71.3	75.4	4.1
60 mg	71.1	74.7	3.6

Reviewer Comment

Although istradefylline is associated with a slightly greater mean decline in BP and a slight increase in pulse rate the changes are not clinically significant. There did not appear to be a dose dependent orthostatic change in BP or pulse.

Table 7.31 Mean Change in Systolic BP by Istradefylline Dose and Visit

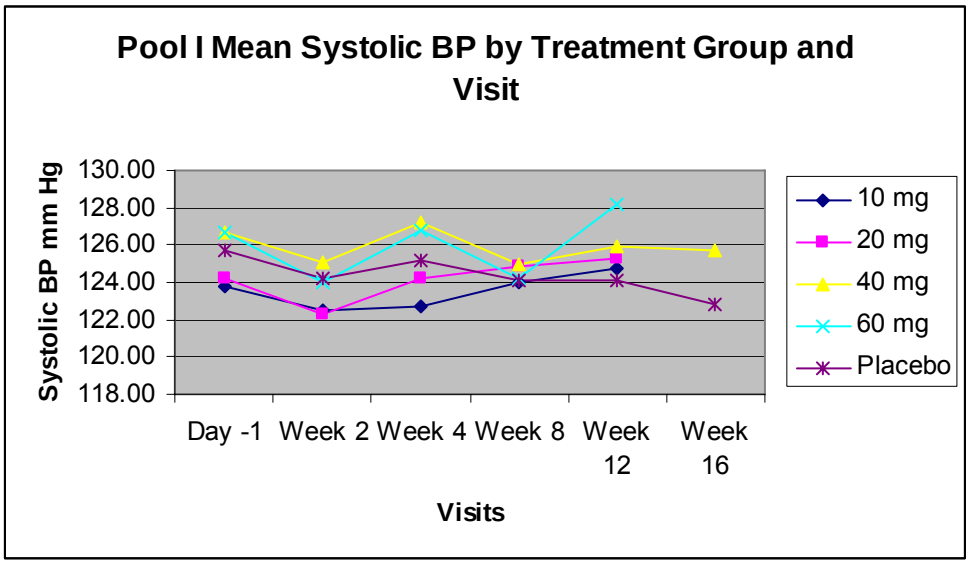
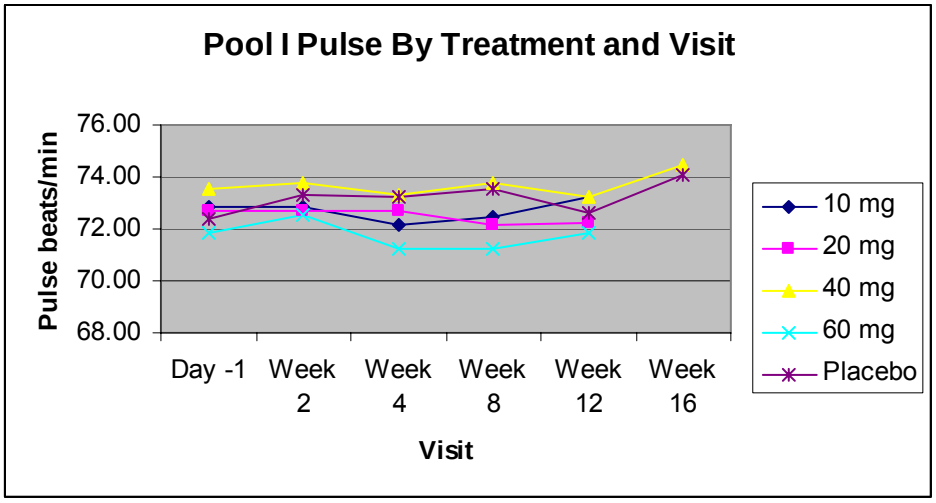


Table 7.32-Mean Change in Pulse by Istradefylline Dose and Visit



*Data from weeks 12-16 (40 mg istradefylline and placebo) is only from data taken from the 6002-EU-007 trial.

There was no significant change in mean systolic BP or pulse in subjects enrolled in controlled clinical trials involving subjects with PD. There was no evidence of a dose dependent effect on BP mean pulse or systolic BP.

Table 7.33-Median Change in Weight 6002-US-006 Study

	Placebo (Wt. in Kg)	20 mg (Wt. in Kg)	60 mg (Wt. in Kg)
Day 1	82.1	74.35	78.9
Week 2	82.1	73.9	79.4
Week 12	81.45	73.5	78.75
Change (wk12-Day1)	-0.65	-0.85	-0.15

The mean change in weight observed in the 6002-US-006 study did not reveal evidence supporting an istradefylline associated change in weight. There did not appear to be a significant effect of istradefylline on median weight loss.

7.2.4 Electrocardiograms (ECGs)

7.2.5 Overview of ECG testing in the development program, including brief review of preclinical results

7.2.6 Thorough QT Study

6002-US-024: A Double-Blind, Randomized, Parallel-Group Study to Define the ECG Effects of Istradefylline Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) Compared to Placebo in Non-Smoking, Healthy, Male and Female Subjects: A Thorough QTc Study

The Sponsor's Conclusion: Results of the Thorough QT Study

Analysis of the data from this thorough QT Study showed no clinically relevant effects on AV conduction, depolarization or cardiac repolarization as measured by the PR, QRS or QTc interval durations. The assay sensitivity of the trial was validated by expected QTc prolongation in the moxifloxacin positive control group. The lack of any gender effect, pharmacodynamic-pharmacokinetic relationship, or QTcI values meeting the outlier criteria for istradefylline also supports the conclusion that istradefylline does not prolong the QTc interval. Istradefylline did not result in clinically relevant ECG effects at doses of 40 mg/day and 160 mg/day at steady state.

Reviewer's Comment

The agency's QT Team reviewed the sponsor's Thorough QT/QTc Study (6002-US-024) on 12/19/2006.

The conclusions of the agency QT team's review:

> "Table 1 provides the largest mean difference of the drug and placebo as well as the 90% confidence interval. This result suggests that istradefylline does not affect QTc duration to a clinically significant degree.

Table 7.34

Table 1. FDA Analysis: Maximum Mean Effect By Dose Group for ddQTcI

Dosing Regimen	Time (h)	ddQTcF (msec)	2-sided 90% UB (msec)
KW-6002 40mg	4	1.22	(-2.91, 7.24)
KW-6002 160mg	5	3.34	(-2.66, 8.24)

7.2.7 Phase 3 Study ECG Analysis

(b) (4) conducted a centralized analysis of the digitally transmitted ECG data from pooled from the phase 3 clinical trials (studies 6002-US-013, 018 and 6002-EU-007). The central ECG analysis included descriptive analysis of HR, PR interval, QRS duration, QT interval (including QTcB and QTcF) and ECG diagnoses, outlier analyses for QT interval parameters, shift tables, regression modeling and analyses of covariance for QTcB interval. The data was analyzed for individual studies and for all 3 studies combined.

7.2.7.1 Selection of studies and analyses for overall drug-control comparisons

Phase 3 Study ECG Analysis

(b) (4) conducted a centralized analysis of the digitally transmitted ECG data from pooled from the phase 3 clinical trials (studies 6002-US-013, 018 and 6002-EU-007). The central ECG analysis included descriptive analysis of HR, PR interval, QRS duration, QT interval (including QTcB and QTcF) and ECG diagnoses, outlier analyses for QT interval parameters, shift tables, regression modeling and analyses of covariance for QTcB interval. The data was analyzed for individual studies and for all 3 studies combined.

7.2.7.2 Standard analyses and explorations of ECG data

7.2.7.2.1 Analyses focused on measures of central tendency

Phase 3 Study ECG Analysis (studies 6002-US-013, 018 and 6002-EU-007)

Heart rate

There mean heart varied by < 3 BPM among any of the 5 treatment groups. The only statistically significant change in the istradefylline treated group occurred the 40 mg/day group at week 12. This was the only time point change that was statistically significant, the changes at other time points varied in direction and was not statistically significant.

P-R Interval

The mean PR interval varied within treatment groups and between treatment groups at the four treatment time points by less than 8 msec. The change in PR interval from baseline was less than 3 msec in all three groups at all time points and none of the changes were statistically significant.

QT/QTc

The mean QT and QTc varied within treatment groups and between treatment groups at the four treatment time points by less than 8 msec. The change in QT and QTc interval was no greater than 6 msec at any time points in any group. The was no significant patter of change in any treatment group except for the 40 mg group, in which QT, QTcB and QTcF was consistently negative. The decrease was statistically significant for QTcB at weeks 4 and 12 weeks in the 40 mg group, and for QTcF at weeks 4 and 8. The only statistically significant change was reported in the placebo group at week 16, where a statistically significant decrease of both QTcB and QTcF, these changes were not clinically significant.

7.2.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

There were rare instance of QT or QTc > 500 ms but the distribution of QT, QTcB and QTcF did not differ significantly between the groups. The only statistically significant change in the istradefylline group compared to placebo was reported in both the group mean analyses and the regression modeling, there was increase of QTcB in the 40 mg/day istradefylline group at Week 16 ($p = 0.03$) only. The changes in QTcB were both negative and positive in the 40 mg/day group at various time points, and decreases in QTcB and QTcF were more frequent than increases for all 3 istradefylline dose groups, suggesting the mean increase in QTcB was not a clinically significant finding. The ECG data from weeks 12-16 is data from the 6002-EU-007 study only since the US-013 and US-018 studies ended after 12 weeks. The smaller number of subjects at week 16 may account for the percent change in ECG parameters appearing greater at the week 16 visit.

Table 7.35-Summary Statistics for Change in QTcF from Baseline (Kyowa Table)

			QTcF<450		450<=QTcF<480		480<=QTcF<500		QTcF>=500	Total
Cohort	Time	N	Percent	N	Percent	N	Percent	N	Percent	N
Placebo	Week 4	369	97.4	10	2.6	0	0.0	0	0.0	379
Placebo	Week 8	362	96.5	12	3.2	1	0.3	0	0.0	375
Placebo	Week 12	254	97.7	6	2.3	0	0.0	0	0.0	260
Placebo	Week 16	136	97.8	3	2.2	0	0.0	0	0.0	139
Placebo	Overall	1121	97.2	31	2.7	1	0.1	0	0.0	1153
Istradefylline 10 mg/day	Week 4	143	98.6	1	0.7	1	0.7	0	0.0	145
Istradefylline 10 mg/day	Week 8	134	97.1	4	2.9	0	0.0	0	0.0	138
Istradefylline 10 mg/day	Week 12	146	96.7	4	2.6	0	0.0	1	0.7	151
Istradefylline 10 mg/day	Overall	423	97.5	9	2.1	1	0.2	1	0.2	434
Istradefylline 20 mg/day	Week 4	243	98.4	3	1.2	0	0.0	1	0.4	247
Istradefylline 20 mg/day	Week 8	237	97.5	5	2.1	0	0.0	1	0.4	243
Istradefylline 20 mg/day	Week 12	258	98.1	4	1.5	0	0.0	1	0.4	263
Istradefylline 20 mg/day	Overall	738	98.0	12	1.6	0	0.0	3	0.4	753
Istradefylline 40 mg/day	Week 4	287	96.6	8	2.7	1	0.3	1	0.3	297

Istradefylline 40 mg/day	Week 8	271	96.4	10	3.6	0	0.0	0	0.0	281
Istradefylline 40 mg/day	Week 12	143	96.6	4	2.7	0	0.0	1	0.7	148
Istradefylline 40 mg/day	Week 16	151	97.4	3	1.9	1	0.6	0	0.0	155
Istradefylline 40 mg/day	Overall	852	96.7	25	2.8	2	0.2	2	0.2	881
Entacapone	Week 4	134	99.3	1	0.7	0	0.0	0	0.0	135
Entacapone	Week 8	130	99.2	1	0.8	0	0.0	0	0.0	131
Entacapone	Week 16	140	97.2	3	2.1	1	0.7	0	0.0	144
Entacapone	Overall	404	98.5	5	1.2	1	0.2	0	0.0	410
Total		3538	97.4	82	2.3	5	0.1	6	0.2	3631

Table 7.36-Summary Statistics for Change in QTcF from Baseline (Kyowa Table)

			QTcF-Baseline<0		0<=QTcF-Baseline<30		30<=QTcF-Baseline<60		QTcF-Baseline>=60	Total
Cohort	Time	N	Percent	N	Percent	N	Percent	N	Percent	N
Placebo	Week 4	171	45.2	187	49.5	19	5.0	1	0.3	378
Placebo	Week 8	189	50.7	166	44.5	18	4.8	0	0.0	373
Placebo	Week 12	126	48.5	120	46.2	13	5.0	1	0.4	260
Placebo	Week 16	83	60.6	51	37.2	3	2.2	0	0.0	137
Placebo	Overall	569	49.6	524	45.6	53	4.6	2	0.2	1148
Istra 10 mg	Week 4	77	53.1	57	39.3	10	6.9	1	0.7	145
Istra 10 mg	Week 8	73	52.9	61	44.2	3	2.2	1	0.7	138
Istra 10 mg	Week 12	69	45.7	76	50.3	5	3.3	1	0.7	151
Istra 10 mg	Overall	219	50.5	194	44.7	18	4.1	3	0.7	434
Istra 20 mg	Week 4	115	46.6	120	48.6	11	4.5	1	0.4	247
Istra 20 mg	Week 8	115	47.3	115	47.3	11	4.5	2	0.8	243
Istra 20 mg	Week 12	124	47.1	126	47.9	11	4.2	2	0.8	263
Istra 20 mg	Overall	354	47.0	361	47.9	33	4.4	5	0.7	753
Istra 40 mg	Week 4	161	54.9	121	41.3	10	3.4	1	0.3	293
Istra 40 mg	Week 8	145	52.2	118	42.4	15	5.4	0	0.0	278
Istra 40 mg	Week 12	77	52.4	68	46.3	2	1.4	0	0.0	147
Istra 40 mg	Week 16	82	53.9	63	41.4	5	3.3	2	1.3	152
Istra 40 mg	Overall	465	53.4	370	42.5	32	3.7	3	0.3	870
Entacapone	Week 4	60	45.8	68	51.9	3	2.3	0	0.0	131
Entacapone	Week 8	55	43.7	66	52.4	5	4.0	0	0.0	126
Entacapone	Week 16	63	45.3	69	49.6	6	4.3	1	0.7	139
Entacapone	Overall	178	44.9	203	51.3	14	3.5	1	0.3	396
Total		1785	49.6	1652	45.9	150	4.2	14	0.4	3601

7.2.7.2.3 Marked outliers and dropouts for ECG abnormalities

No subjects withdrew from any of the pivotal studies based solely on changes in ECG parameters. A single subject treated with istradefylline withdrew from the 6002-US-018 study because of new atrial fibrillation.

7.2.8 Immunogenicity

Not applicable

7.2.9 Human Carcinogenicity

Istradefylline is not considered carcinogenic in humans in dose of 20 mg – 40 mg per day. Animal data from a 2-year study in mice and rats at doses producing 11-56 times the exposure predicted in humans at 20mg to 40 mg daily.

Istradefylline was not genotoxic or mutagenic in the standard battery of genotoxicity screens. Istradefylline was not mutagenic in the in vitro reverse mutation assay in bacteria. Istradefylline was not clastogenic in the in vitro chromosomal aberration assay in Chinese Hamster Lung cells or in the in vivo micronucleus study in mice. Istradefylline did not induce unscheduled DNA synthesis in the rat liver in vivo/in vitro assay.

7.2.10 Withdrawal Phenomena and/or Abuse Potential

Studies conducted in rats did not reveal evidence for dependency or abuse. There have been no human studies that have examined the potential for human dependency of abuse. There had been no evidence form controlled clinical trials to suggest istradefylline has potential for dependency or abuse in humans. Impulse control disorders, hypersexuality and obsessive-compulsive behaviors were included in the sponsor's adverse event reports but medication-seeking behavior or hedonistic homeostatic dysregulation syndrome was absent.

7.2.11 Human Reproduction and Pregnancy Data

A single pregnancy occurred in an 18-year-old healthy volunteer who participated in the 6002-US-024 study in (b) (6). The subject received istradefylline 40 mg/day. Although her serum hCG was negative at the screening visit (day -2), on day 15 of the study the subject's hCG was positive and she was immediately discontinued from the study. Pregnancy was confirmed during an obstetrical examination and after counseling, the subject decided to

continue the pregnancy. The estimated date of confinement for the pregnancy was (b) (6) . Unfortunately, the subject last contact with the study site was (b) (6); the outcome of the pregnancy remains unknown.

7.2.12 Assessment of Effect on Growth

Not applicable

7.2.13 Overdose Experience

The cumulative experience regarding overdose is insufficient assess adverse effects specific to istradefylline overdose. The sponsor's case reports of istradefylline are summarized below.

Case Mfr. report # KW-6002- (b) (6)

The subject is a 70 year-old male with PD, who was receiving istradefylline 40 mg/day in an open-label study. Concomitant medications included levodopa, entacapone, simvastatin, metoprolol, isosorbide, aspirin, clopidogrel, escitalopram, pramipexole, and rivastigmin. The subject took his usual daily dose of study medication and his entire dialy allotment of his concomitant medications all at once in the morning. He developed sudden and severe dyskinesia with confusion and agitation. The subject was treated in a local emergency room with lorzapam and diphenhydramine. Medcations were withheld and the subject recovered by the next day.

Case Mfr. report # KW-6002- (b) (6)

A 54-year-old man with PD receiving istradefylline 40 mg/day in an open label study took 6 tables of study medication and consumed 2 alcoholic beverages. The subject developed hallucinations, agitation and worsening dyskinesia. He was taken to a local hospital later that night and he was released 9 hours later after his condition improved. Concomitant medications included pergolide 25 mg (reviewer assumes pergolide 2.5 mg was the actual dose) and co-enzyme Q-10 1200 mg/day.

Non-trial Participant

A 3-year-old male child of a study participant ingested a single 40 mg tablet of istradefylline without reported adverse effects. The child was hospitalized, treated with G.I. decontamination and he was admitted to the hospital for observation and discharges without reported adverse effects.

7.3 Postmarketing Experience

Not Applicable

7.4 Adequacy of Patient Exposure and Safety Assessments

Exposure is adequate in the short-term and long-term studies at the 40 mg/day dose meet ICH guideline for adequate exposure at 6 months and 12 months. At the 60 mg/day dose long-term exposure of only 29 subjects at > 12 months does not meet ICH guidance E1A guidelines suggesting 100 subjects or more exposed for at least12 months.

7.4.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.4.1.1 Study type and design/patient enumeration

Please see the Exposure and Efficacy portions of this review.

7.4.1.2 Demographics

Table 7.37-The Sponsor's Table summarizing Demographic data in Pool I

Table 8.H-16 Demographic Characteristics: Pool I

Variable Statistic	Number (%) of Subjects					
		Istradefylline				
	Placebo (N=561)	10 mg/day (N=153)	20 mg/day (N=427)	40 mg/day (N=440)	60 mg/day (N=155)	Total (N=1736)
Age (years)						
Mean	63.0	63.2	64.2	62.1	63.5	63.1
SD	9.54	8.89	9.64	9.23	10.08	9.50
Median	63.0	64.0	64.0	62.0	65.0	63.0
Minimum	36	43	35	35	36	35
Maximum	87	84	87	84	83	87
Gender						
Male	360 (64.2)	103 (67.3)	283 (66.3)	276 (62.7)	106 (68.4)	1128 (65.0)
Female	201 (35.8)	50 (32.7)	144 (33.7)	164 (37.3)	49 (31.6)	608 (35.0)
Race/Ethnicity						
Caucasian	479 (85.4)	142 (92.8)	400 (93.7)	373 (84.8)	141 (91.0)	1535 (88.4)
Black	6 (1.1)	3 (2.0)	6 (1.4)	3 (0.7)	4 (2.6)	22 (1.3)
Asian	42 (7.5)	3 (2.0)	9 (2.1)	39 (8.9)	2 (1.3)	95 (5.5)
Hispanic	25 (4.5)	3 (2.0)	4 (0.9)	20 (4.5)	4 (2.6)	56 (3.2)
Other [a]	9 (1.6)	2 (1.3)	8 (1.9)	5 (1.1)	4 (2.6)	28 (1.6)
Height (cm)[b,c]	169.70 ± 10.362	171.10 ± 9.450	171.58 ± 9.985	169.17 ± 10.481	172.84 ± 10.476	170.43 ± 10.293
Weight (kg)[c]	77.33 ± 17.759	83.57 ± 16.509	79.12 ± 17.804	77.11 ± 17.977	78.86 ± 16.782	78.40 ± 17.708
BMI (kg/m^2)[c]	26.65 ± 4.764	28.51 ± 5.243	26.75 ± 5.095	26.85 ± 5.368	26.28 ± 4.560	26.86 ± 5.053
Current Smoker						
Yes	34 (6.1)	3 (2.0)	20 (4.7)	22 (5.0)	7 (4.5)	86 (5.0)

[a] "American Indian" modality is not used in all studies, this modality is presented in "Other".
[b] At screening visit.
[c] Mean ± SD.
BMI = body mass index; SD = standard deviation
Source: Table S.1.3.1

There was not a significant difference between treatment groups in age, height or weight. Males out numbered females by about a 2:1 margin, which is consistent with the gender distribution of PD. Caucasians also out numbered out numbered all other ethnic groups by a large margin, which is also consistent with the known ethnic distribution of PD. The number of smokers were also small which is typical among patients with PD. The distribution of smokers was similar between treatment groups and the small differences are unlikely to alter the safety or efficacy data. The demographic factors features were similar for the other studies but in pools III and

7.4.1.3 Extent of exposure (dose/duration)

Table 7.38-Pool I Exposure Controlled Clinical Trials in PD

	N Exposed	Exposure Days	Mean Exposure Days	Median Exposure Days	Person-years Exposure
Istradefylline 10 mg/day	159	12182	79.62	84	33.38
Istradefylline 20 mg/day	158	34999	79.54	84	95.89
Istradefylline 40 mg/day	442	39295	89.31	86	107.66
Istradefylline 60 mg/day	446	11619	74.96	84	31.83
Placebo	155	48241	85.08	84	132.17
Total Istradefylline Exposure	1205	98095			268.75

Table 7.39-Pool V Exposure All Indications Tested (exposure < 3 months)

	N Exposed	Mean Exposure Days	Median Exposure Days	Total Exposure Day	Person-years
Placebo	926	71.46	83	66172	181.29
Istradefylline 10 mg/day	153	79.62	84	12182	33.38
Istradefylline 20 mg/day	466	79.48	84	37036	101.47
Istradefylline 40 mg/day	741	74.80	84	55426	151.85
Istradefylline 60 mg/day	155	74.96	84	11619	31.83
Istradefylline 80 mg/day	12	26.42	28	317	0.87
Istradefylline 120 mg/day	136	35.52	42	4831	13.24
Entacapone 200 mg	152	100.96	112	15346	42.04
Total Istradefylline exp	1663				332.63

Ex**posure in long-term open label clinical trials**

The sponsor described 3 methods they calculated exposure in pool II. Closure of the initial long-term clinical trials resulting from the clinical hold that lasted 1 year appears to be the primary reason for using different methods of analyzing exposure in pool II. Continuous Exposure Method I was preferred by the reviewer because it avoids the problem encountered in continuous exposure method 2 of counting subjects twice and it avoids the cumulative exposure problem of ignoring a 1-year interruption in therapy for some of the subjects.

• **Continuous Exposure Method 1** (excludes 6002-INT-001 and 6002-US-025 data for subjects who entered Study 6002-INT-001 following Study 6002-US-007 enrollment). Thus, for this method, only 6002-US-007 data was analyzed for subjects who participated in both long-term studies. There are a total of 1585 analyzed subjects (1301 in the 40 mg/day maximal dose group and 284 in the 60 mg/day maximal dose group).

• **Continuous Exposure Method 2** (includes 6002-INT-001 and 6002-US-025 data as a "separate subject" for subjects who entered Study 6002-INT-001 following Study 6002-US-007 enrollment). Thus, for this method, a subject who participated in both Studies 6002-INT-001 and 6002-US-007 were counted as 2 subjects. There are a total of 1737 analyzed subjects (1453 in the 40 mg/day maximal dose group and 284 in the 60 mg/day maximal dose group).

• **Cumulative Exposure Method** (combines 6002-US-025, 6002-INT-001 and 6002-US-007 data for subjects with exposures in Study 6002-US-007 and one or more of the other studies). Thus, for this method, the gap between 6002-INT-001 and 6002-US-007 is ignored for purposes of analyses. As for Continuous Exposure Method 1, there are a total of 1585 unique subjects (1301 in the 40 mg/day maximal dose group and 284 in the 60 mg/day maximal dose group).

Table 7.40-Pool II Exposure Long-Term Studies in Subjects with PD Continuous Exposure Method 1 (including 4 month update)

	N Exposed	Mean Exposure Weeks	Mean Days	Median Exposure Weeks	Person-years
Istradefylline 40 mg/day	1184	24.23	169.61	19.85	551.5
Istradefylline 60 mg/day	284	29.18	204.26	29.90	158.8
Total Istradefylline	1468	25.19	176..33	23.10	710

Table 7.41-Reviewer's Analysis Continuous Exposure Pool II Using The Sponsor's Updated Tabulation Dataset

TRMAXGRP	N(pt days)	Sum(pt days)	Mean(pt days)	Median(pt days)	Person years
Istradefylline 40 mg/day	1453	409036.8	281.51	363.3	1120.65
Istradefylline 60 mg/day	284	58009	204.26	209.5	158.93
Total	1737				1279.45

Table 7.42-Comparison of Exposure of Istradefylline to ICH Guideline

	ICH Guideline N	Istradefylline 40 mg/day N	Istradefylline 60 mg/day N	Total Istradefylline Either Dose N
6 Months	300-600	1102	162	1264
12 Months	100	342	29	371
Total	1500	1453	284	1737

Reviewer Comment

Exposure is adequate and meets ICH recommended guideline E1A, "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions".

7.4.1.4 Post-marketing experience

Not Applicable

7.4.1.5 Literature

7.4.2 Adequacy of Overall Clinical Experience

Adequate.

7.4.3 Adequacy of Special Animal and/or In Vitro Testing

Appears adequate but the reader is referred to the Pharmacology-Toxicology review conducted by Dr. Terry Peters, DVM.

7.4.4 Adequacy of Routine Clinical Testing

Adequate

7.4.5 Adequacy of Metabolic, Clearance, and Interaction Workup

Adequate but the reviewer is referred the Clinical Pharmacology review for details.

7.4.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.4.7 Assessment of Quality and Completeness of Data

The quality and completeness of the safety data was adequate. The efficacy data collection and overall analysis was adequate. Some of the efficacy data attempted to highlight positive but not clinically meaningful outcomes such as reporting the results of individual positive study visits in the face of negative result at the conclusion of the study.

7.4.8 Additional Submissions, Including Safety Update

Kyowa submitted a 4-month safety update to the NDA application on the sponsor's date of August 7, 2007. The update primarily affected the safety database, additional efficacy information included a final study report for the 6002-0406 study, which was conducted exclusively in Japan. The results of the 6002-0406 study was reported in the reviewer's integrated efficacy review. Exposure and adverse event data was updated to the cutoff date of May 31, 2007. Safety data pools II (long-tern studies) and V (double blind studies all indications) were the two pools affected by the updates. A new safety pool VI was created and included two data from two completed studies. Study 6002-US-201 conducted in subjects with Restless Legs Syndrome (RLS) and it was not relevant to the NDA application therefore only the data for this study was only reviewed as part of the safety analysis of pool V data. Study 6002-US-051 was a monotherapy trial of istradefylline in subjects with earlier stages of Parkinson's and differs from the indication for this application. The efficacy results of this study are discussed in the reviewers efficacy review. Updated narratives for subjects who died or became pregnant were included through May 31, 2007. The data from the updated data regarding exposure, all classifications of adverse events and narratives were included in the reviewers analysis.

7.5 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most important limitation of the adverse event data is the potential association between Impulse Control Disorders (ICD) and istradefylline. If approved, a simple trial incorporating questionnaires to monitor for ICDs in an istradefylline cohort compared to placebo would be ideal. This is important for two reasons, first istradefylline is a "first in its class medication" and second, the mechanism of action of istradefylline should in theory, be less likely to cause ICDs.

7.6 General Methodology

7.6.1 Pooling Data Across Studies to Estimate and Compare Incidence

The ISS data pooling strategy is described in detail in the safety portion of this review. The rational for the sponsors method forming and analyzing the data pools is acceptable. The efficacy review was based on individual study reviews except of dose-response analysis, which is discussed in detail in the efficacy portion of this review. Pooled efficacy data across studies was analyzed in the Biopharmacology review looking at dose response data and there did not appear to be a dose or exposure response related to the primary efficacy endpoint.

7.6.1.1 Pooled data vs. individual study data

The review of adverse events found that the review of individual and pooled safety data were consistent revealing the same type and approximately the same frequency of adverse events. The efficacy review was based on the outcome of individual controlled trials and the results are discussed in the efficacy portion of this review.

7.6.1.2 Explorations for dose dependency for adverse findings

Table 7.43-Overview of TEAEs Reported in Pool I (Kyowa Table)

Table 8.H-38 Overview Summary of TEAEs: Pool I

Subjects	Number (%) of Subjects					
		Istradefylline				
	Placebo (N=561)	10 mg/day (N=153)	20 mg/day (N=427)	40 mg/day (N=440)	60 mg/day (N=155)	Total (N=1175)
Subjects with any TEAE	**413 (73.6)**	**126 (82.4)**	**346 (81.0)**	**346 (78.6)**	**133 (85.8)**	**951 (80.9)**
Subjects with serious TEAE	19 (3.4)	6 (3.9)	19 (4.4)	23 (5.2)	4 (2.6)	52 (4.4)
Subjects with any TEAE leading to discontinuation	33 (5.9)	5 (3.3)	27 (6.3)	30 (6.8)	16 (10.3)	78 (6.6)
Subjects with any related [a] TEAE	285 (50.8)	93 (60.8)	243 (56.9)	251 (57.0)	98 (63.2)	685 (58.3)
Subjects with any severe TEAE	58 (10.3)	18 (11.8)	51 (11.9)	56 (12.7)	19 (12.3)	144 (12.3)
Deaths	4 (0.7)	1 (0.7)	0	2 (0.5)[b]	0	3 (0.3)

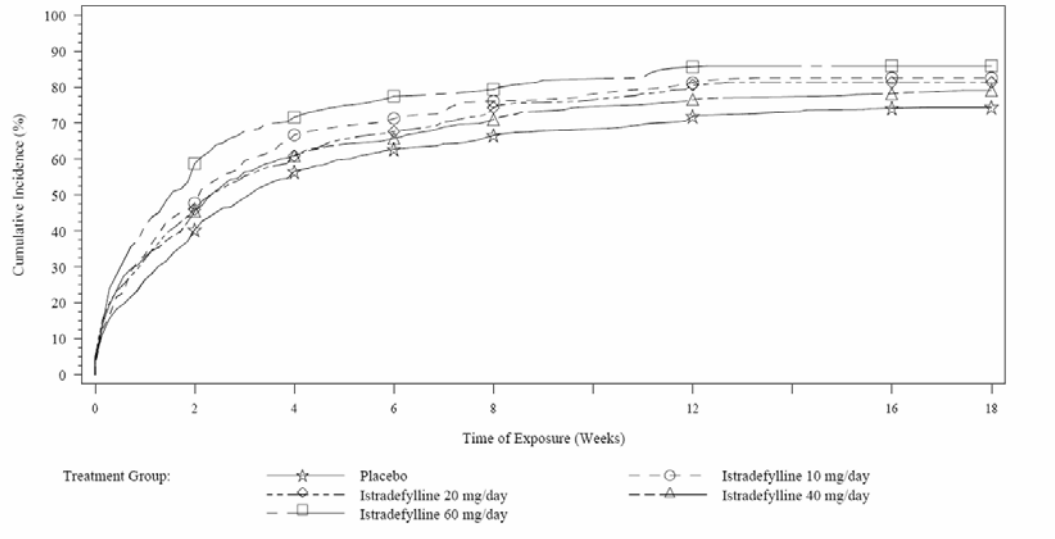
[a] Related = includes probably and possibly study drug related.
[b] Subject (b) (6) in Study 6002-US-018 who died 52 days after the last dose of study drug, is not included.
Source: Table S.2.2.1.1

In general, TEAEs were greater in the istradefylline treated groups. There was a clear dose effect in the istradefylline treated groups for TEAEs leading to discontinuation. There were no significant differences between istradefylline and placebo with regards to deaths, serious or severe TEAEs.

Dose comparisons for efficacy and specific adverse events are incorporated in this review. Dose response relationships for efficacy any adverse effects are discussed in the body this review and in the clinical pharmacology and biometrics reviews.

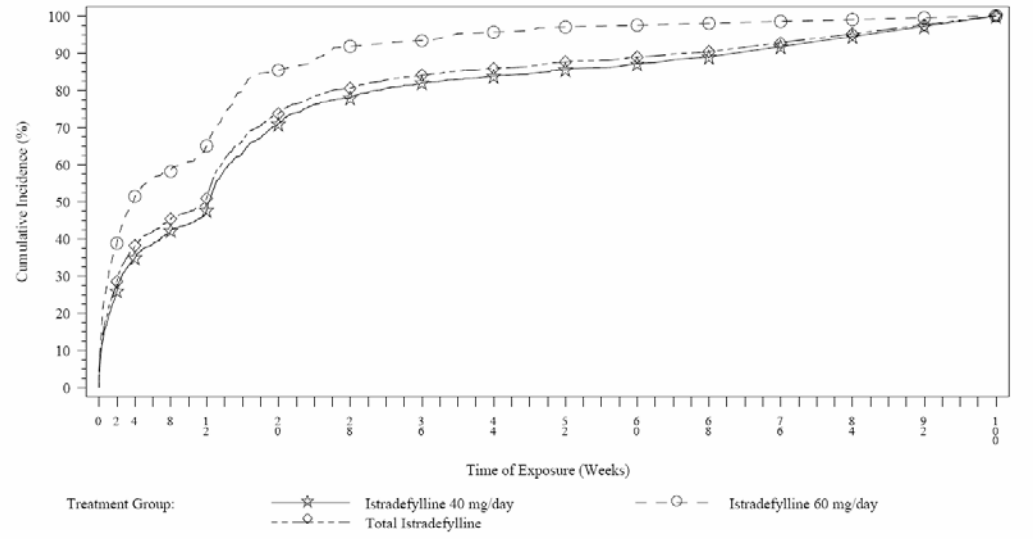
7.6.1.3 Explorations for time dependency for adverse findings

Table 7.44-Kaplan-Meier Analysis – Cumulative Incidence of Overall TEAEs as a Function of Duration of Exposure – Safety Analysis Set –Pool I (Kyowa Table)



Approximately half of subjects in all groups in Pool I had their first TEAEs by Week 2. The rate of TEAE decreased after Week 2 and the rate of first occurrence of new TEAEs was the same for istradefylline (regardless of dose) and placebo.

Table 7.45-Kaplan-Meier Analysis – Cumulative Incidence of Overall TEAEs as a Function of Duration of Exposure – Safety Analysis Set –Pool II (Continuous Exposure Method 1) (Kyowa Table)



Approximately half of subjects reported their first TEAE by Week 12. The rate of first TEAE occurrence decreased and beyond Week 20 accounting for less than 20% of all first

occurrences of TEAEs in the long-term follow-up. The cumulative incidence of subjects with any TEAE showed a biphasic upslope, in cumulative incidence in the first few weeks of exposure and a second increase at approximately 12 weeks of exposure. This second upslope may be caused by subjects on istradefylline in double-blind studies moving to one of the open-label.

7.6.1.4 Explorations for drug-demographic interactions

The sponsor explored the following potential drug-demographic interactions:

- Drug-Age (≤ 65, ≥ 65 and ≥ 75 years)
- Drug-Gender (M vs. F)
- Drug-Race Caucasian vs. non-caucasian)
- Drug-BMI (≤ 35 and ≥ 35 kg/m^2)
- Drug-Smoking Status

The frequency of TEAEs increased slightly with increasing age for all doses of istradefylline and placebo. Overall the number of TEAEs increased proportionally for both the placebo and istradefylline groups for a given age category. The pattern and types of TEAEs were similar in all 3 age groups. Phase I pK studies did not find significant differences in pK parameters with advancing age and no dose adjustment is recommended for the elderly.

TEAEs were more common in females compared to males in general, however the differences in the proportions of subjects with TEAEs between the istradefylline dose groups and placebo group were comparable across the genders. At least 1 TEAE was reported for females at a frequency of 88.0%, 87.5%, 88.4% and 83.7%, respectively for the 10, 20, 40, and 60 mg/day istradefylline groups and 81.1% on placebo. At least 1 TEAE was reported for males at a frequency of 69.4% on placebo and 79.6%, 77.7%, 72.8% and 86.8%, respectively for the 10, 20, 40, and 60 mg/day istradefylline groups. The pattern of TEAEs were similar in both genders with dyskinesia and nausea being the most commonly reported adverse events.

The number of non-caucasian study participants were small consistent with the demographics of Parkinson's which most commonly affects caucasian males, Cross study comparisons did not find that non-caucasian subjects were more likely to experience a TEAE or withdraw from the study because of an AE.

The number of subjects with a BMI ≥ 35 kg/m^2 were small in number. BMI did not appear to alter the number or type of TEAEs reported during clinical trials

The overall pattern of TEAEs was comparable for current smokers and for nonsmokers/ former smokers although the number of subjects who were smokers was very small. The low number of study subjects who were smokers (5%) is consistent with literature reports of the low prevalence of smoking in Parkinson's disease patients. The effect of cigarette smoking on

istradefylline systemic exposure was evaluated in a comprehensive population pharmacokinetic analysis and in a focused Phase 1 study. Steady-state istradefylline exposure was about 38% to 42% lower in smokers compared to non-smokers.

7.6.1.5 Explorations for drug-disease interactions

Istradefylline was studies in subjects with early PD (Hoehn and Yahr stage 1-2.5) but the trial results did not attain statistically significant results on the primary outcome measure (change in UPDRS part 3). The efficacy of istradefylline in subjects with more advanced PD the indication under review. Clinical trials data in subjects with advance PD (motor response fluctuations) have yielded mixed positive and negative results. The clinical and dose response analysis by clinical pharmacology and biometrics indicate the treatment effect is small and not clinically significant.

Table 7.46-Pool I Dyskinesia By Hoehn & Yahr Stage of Parkinson's Disease

AE Term	Placebo	Istrad 10 mg/d	Istrad 20 mg/d	Istrad 40 mg/d	Hoehn & Yahr Stage
Dyskinesia	22 (10.0)	21 (21.9)	24 (15.2)	26 (15.6)	H & Y <3
Dyskinesia	26 (16.6)	10 (22.2)	23(27.4)	28 (24.6)	H & Y=3
Dyskinesia	6 (14.3)	2 (16.7)	4 (18.2)	8 (26.7)	H & Y≥ 4

Dyskinesia was not associated with a significant dose response relationship but there is a disease response relationship between dyskinesia and dose of istradefylline especially at the 20 mg/day dose and above. There were only a few subjects with Hoehn and Yahr stage 4 and above and it is difficult to draw meaningful conclusions with such a small number of subjects.

7.6.1.6 Explorations for drug-drug interactions

Overview of Metabolism

In vitro studies indicate that istradefylline is predominantly metabolized via CYP3A4 with minor contributions from other isoenzymes such as CYP1A1/1A2, CYP2C9, CYP2C18, and CYP 2D6. Additionally, istradefylline is a moderate CYP3A4 inhibitor at doses 2- to 4-fold greater than the clinically recommended doses (20 to 40 mg/day). Since the inhibitory effect is unknown at 40 mg/day, caution must be used when administering istradefylline at this dose with narrow therapeutic index drugs metabolized via the CYP3A4 pathway. Ketoconazole had no effect on istradefylline mean C_{max}, although the mean AUC increased by 2.5-fold. The 2.5-fold increase in AUC indicates that a 20 mg dose can be safely administered with ketoconazole. The sponsor recommends (b) (4)

Atorvastatin

The pharmacokinetic interaction between 40 mg/day istradefylline and 40 mg atorvastatin was evaluated in a separate pK study. The administration of multiple doses of 40 mg/day

istradefylline with a single 40 mg dose of atorvastatin, increased atorvastatin C_{max} and AUC by 1.5-fold versus administration of atorvastatin alone.

Smokers

In a clinical study, steady-state systemic exposure of istradefylline was 42% lower in smokers compared to age, gender and body-weight matched non-smokers. In a population pharmacokinetic analysis across several Phase 1, 2 and 3 studies, cigarette smoking was also identified as a significant factor that increased istradefylline clearance.

Other Parkinson's Drugs

Subjects on istradefylline who were taking dopamine agonists reported similar frequencies of TEAEs as those on placebo (82.9%, 82.1%, 81.7%, and 87.3% of subjects on 10, 20, 40, and 60 mg/day of istradefylline, respectively, and 76.1% of subjects on placebo). The frequency of any TEAE of the nervous system disorders SOC was greater in the subgroup of subjects taking dopamine agonists (except for the 10 mg/day istradefylline group), compared to subgroup of subjects who were not. Similarly, TEAEs of dyskinesia were more frequent for all groups in subjects who were taking dopamine agonists.

Conclusion

There were no clinically relevant differences in the TEAE profile of istradefylline compared to that of placebo f extrinsic factors (current smoking status and time since initiation of levodopa) and concomitant medication use (anti-hypertensive, dopamine agonists, COMT inhibitors, and combination of dopamine agonists and COMT inhibitors).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Istradefylline is administered once daily with or without food. There were no clinically relevant differences found in subgroup analyses based on food consumption for the 3 istradefylline dose groups or placebo groups in Pool I. The administration of istradefylline in the fasted state was not associated with a clinically meaningful increase in subjects with TEAEs of nausea. The lack of a clinically significant interaction in the sponsor's subgroup analyses or in the clinical pharmacology analysis supports the sponsor's conclusion that istradefylline may be administered with or without food.

8.2 Special Populations

8.2.1 Hepatic Impairment

Hepatic impairment Child-Pugh B category, who were non-smokers had approximately a 3.3 X greater exposure compared to health subjects. The T1/2 more than doubled in non-smokers with hepatic impairment. (b) (4) .

8.2.2 Smokers

Smoking cigarette induces the metabolism of istradefylline through the CYP1A1/1A2 pathways, as a result clearance is increased significantly, reducing the steady state AUC_{0-24} of istradefylline by 38%. Pharmacokinetic and pharmacodynamic data indicate a 40 mg/day dose of istradefylline in a smoker results in an efficacy response that is similar to the response obtained with a 20-mg/day dose in a non-smoker.

8.3 Pediatrics

The sponsor was granted a pediatric waver. The sponsor did not perform any systematic evaluations of istradefylline in pediatric age subject since Parkinson's is rare in the pediatric population.

8.4 Advisory Committee Meeting

8.5 Literature Review

8.6 Post-marketing Risk Management Plan

8.7 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

Safety Summary

The sponsor's assessment of safety appears to be adequate and it was performed with reasonable diligence. There were no safety related events that were serious or life threatening. The incident of death was similar for placebo and istradefylline treated groups. The cause of death was consistent with expected causes of death for the age group recruited into the studies and disability caused by PD. Deaths that occurred in uncontrolled long-term trials were similar in rate and cause of death compared to reports in the published medical literature.

In general, TEAEs were more common in the istradefylline group compared to placebo. The percentage of serious adverse events that occurred in controlled clinical trials were similar for the placebo and treatment groups. More subjects in the istradefylline treated groups discontinued participation in their respective clinical trial compared to placebo. Dyskinesia, Parkinson's symptoms and nausea were the most commonly given reasons for withdrawal from the trial. Analysis of TEAEs by preferred terms, higher level, higher-level group terms, system organ class and analysis of standardized MedDRA queries (SMQ) did not find a pattern of a previously not described serious or common TEAE.

The most common treatment emergent adverse events were dyskinesia, nausea and dizziness. Of these, nausea demonstrated a clear dose-response relationship up to the highest dose of 60 mg/day. Dyskinesia was greater in all of the istradefylline treated groups without a clear dose response relationship. There is a suggestion for a disease severity (measured by Hoehn & Yahr scale)-relationship with dyskinesia at the 40 mg/day dose in the pool 1 data but the number of subjects with Hoehn and Yahr stage 4 PD or greater (most severe) was small, making it difficult to interpret.

There were no significant changes in vital sign parameters recorded in any of the clinical trials. Study 6002-US-006 monitored for signs of orthostatic hypotension but did not find a significant difference between the placebo and istradefylline for pulse or blood pressure changes.

Clinical laboratory investigations analyzed by measures o central tendency, shift tables, outliers and individual lab parameters or index cases did not find additional evidence for organ system injury clearly associated with istradefylline.

The potential association of istradefylline with impulse control disorders is unexpected based on the drug's mechanism of action. The pivotal trials and long-term safety trials were not design to monitor for this particular TEAE.

Reviewer's Safety Conclusion

Istradefylline does not appear to be associated with sudden or idiosyncratic serious adverse events. The adverse event profile of this medication indicates adverse events can be monitored clinically or with clinical laboratory evaluations. The sponsor should consider adding a plan to evaluate the incidence and severity of impulse control disorders in future clinical trials of istradefylline.

9.2 Recommendation on Regulatory Action

Istradefylline should be " not approvable" based on the failure to demonstrate clinical efficacy at the 10 mg, 40 mg or 60 mg dose in accordance with the agency standard of having two supporting well-controlled clinical trials. Additional information is needed to establish istradefylline improves patient function or how they feel. Studies demonstrating significant improvements in global measures of improvement or severity and improvements in quality of life are important in establishing clinically meaningful improvement in patients with PD. Replication of a statistically significant outcome on the primary efficacy variable for the 40 mg dose is also important in supporting the efficacy claim. The sponsor should demonstrate that the 40 mg/day dose is superior to the 20 mg/day dose or the primary and perhaps a global or quality of life measure.

9.3 Recommendation on Post-marketing Actions

9.3.1 Risk Management Activity

9.3.2 Required Phase 4 Commitments

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

Label Review Istradefylline

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

11 REFERENCES

1. Schwarzschild MS, et al. Targeting adenosine A2A receptors in Parkinson's disease. Trends Neurosci Vol.29 No.11; 647-653.

2. Mahlon R. DeLong, MD; Thomas Wichmann, MD. Arch Neurol. 2007;64:20-24

3. C. Marras, et al. Neurology 2005;64;87-93

4. Poewe W, The natural history of Parkinsons disease. J Neurol. 2006 Dec;253 Suppl 7:VII;2-6

12 6002-US-005

12.1 Clinical Trial Design

Study Title:

A 12-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study of the Efficacy of 40 mg/day KW-6002 as Treatment for Parkinson's Disease in Patients With Motor Response Complications on Levodopa/Carbidopa Therapy

Test Drug: Istradefylline (KW-6002) 40 mg/day

Indication: Parkinson's Disease

Study Design:

A 12-week, double-blind, randomized, parallel-group, placebo-controlled multicenter study to evaluate safety and efficacy

Protocol Identification: 6002-US-005
Protocol Final Version January 30, 2002

Development Phase: 2B

Study Initiation Date: 23 April 2002 (Date of First Dose)

Study Completion Date: 05 May 2003 (Date of Last Dose)

Report Date: 21 April 2006

Rational as stated by the sponsor

Istradefylline (KW-6002), a novel, potent and highly selective adenosine A2A receptor antagonist synthesized at Pharmaceutical Research Institute of Kyowa Hakko Kogyo Co., Ltd. It is currently under development for PD. Adenosine is understood to provide facilitatory control of gamma-aminobutyric acid (GABA) release from the globus pallidus and striatum (dual modulation of indirect pathway). In PD, inhibition of the adenosine A2A receptor is postulated to attenuate activation of this indirect pathway to treat the motor symptoms of PD. Istradefylline is under investigation as an adjunctive therapy in patients with PD (b) (4) .

13 METHODS AND DISCUSSION

13.1 Study Objectives as Stated by The Sponsor

Primary:

The primary objective of this study was to evaluate the safety and establish the efficacy of 40 mg/day istradefylline for reducing OFF time in subjects with advanced PD treated with levodopa/carbidopa.

Secondary:

The secondary objective of this study was to establish the efficacy of 40 mg/day istradefylline for reducing motor symptoms and improving activities of daily living (ADL) in subjects with advanced PD treated with levodopa/carbidopa.

13.1.1 Study Design

The trial is a 12 week randomized, double blind, placebo controlled design. The plan called for 180 subjects to enroll at 25 sites in the U.S. and Canada. The ratio of subject assignment was 2:1 favoring istradefylline.

Key Inclusion Criteria

- Subjects were at least 30 years-old.
- All subjects must meet the UK brain bank criteria for a diagnosis of PD.
- Subjects were modified Hoehn and Yahr stage II-IV in the OFF state
- Participants must have taken levodopa in combination with a decarboxylase inhibitor for at least one year.
- Subjects must have experienced motor response fluctuations taking at least four doses of levodopa per day

A complete list of inclusion and exclusion criteria is contained in the full protocol located in M 5.3.5.1.3 of this submission.

13.1.2 Endpoints

Primary

Change from baseline in percentage of awake time in the 'Off state at endpoint based on the validly completed patient's 'On/Off diaries.

Secondary Endpoints

The Secondary Response Variables

- Change from baseline in the percentage of awake time spent in the 'Off state at Weeks 2, 4, 8, and 12 based on the validly completed patient's 'On/Off' diaries.
- Change from baseline in the total hours of awake time spent in the 'Off' state at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off diaries.
- Change from baseline in percentage of awake time spent in the 'On' state without dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off' diaries.
- Change from baseline in the total hours of awake time spent in the 'On' state without dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off' diaries.
- Change from baseline in the percentage of awake time spent in the 'On' state with dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off diaries.
- Change from baseline in the total hours of awake time spent in the 'On' state with dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off' diaries.
- Change from baseline in the percentage of awake time spent in the 'On' state with non-troublesome dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off' diaries.
- Change from baseline in the percentage of awake time spent in the 'On' state with troublesome dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off diaries.

- Change from baseline in UPDRS I-IV total score (including 'On' time rating for UPDRS II and UPDRS III subscales), defined as the sum of subscales I, II, III, and IV at Weeks 2, 4, 8, 12, and endpoint.
- Change from baseline in UPDRS II subscale total score in 'On' at Weeks 2, 4, 8, 12, and endpoint.
- Change from baseline in UPDRS III subscale total score in 'On' at Weeks 2, 4, 8, 12, and endpoint.
- Change from baseline in UPDRS III subscale total score in 'Off at Weeks 4, 12, and endpoint.
- Clinical Global Impression Global Improvement at Weeks 2, 4, 8, 12, and endpoint.

Other:

- Pharmacokinetic Parameters

Reviewer Comment

The additional secondary endpoints relating to the ON or OFF state are derived endpoints, which are not materially different from the sponsor's primary efficacy endpoint. The derived secondary endpoint "ON with non-troublesome dyskinesia" is very similar to the amount of awake OFF time.

13.1.3 Data Collection

Primary endpoint data was collected using the Hauser version of a 24-hour Parkinson's disease diary[x]. Subjects rate their motor state and record their response directly onto the diary forms as part of the CRF. Subjects may select only 1 of 5 options that describe their current motor condition broken in 30 minute time periods for the entire 24-hour day. Subjects are required to complete at least 2 diaries per visit, on consecutive days, during the week before their scheduled visit. Diaries completion was forbidden on days when subjects were asked to hold their Parkinson's disease medications. Each subject received training on how to appropriately rate their motor state by reviewing instructional videotapes. The subjects rating was tested and compared with the site investigator's rating of the subject's motor state. The rating performed by the investigator and the subject rating must be at least 80% concordant during an 8-hour test period before the subject was enrolled into the trial.

Diary Validation Rules

A diary was considered invalid if there was > 4 missing or invalid entries (2 hours per 24 hour diary).

If subjects completed 2 valid diaries were average off hours over the 48 hour period was used for the visit. If the subject only completed a single completed diary, it was to calculate the percent of awake off time for the visit.

Reviewer Comment

The sponsor provided their rational for using the change in off from baseline compared to endpoint but they did not state the reason for selecting the change in the percent of the awake on time, as opposed to the change in off hours, which they selected as a secondary endpoint. The protocol mentions site personal performed "Diary Review" but it does not define procedures for query of missing or invalid diary entries at each site. The opportunity to have the study coordinator or investigator review the diary and query subject in person about invalid (double) diary entries was lost.

Additional Procedures

- Vital signs, sitting about 2 hours after a dose of levodopa/carbidopa during a morning "ON" state
- Patient diary review
- Laboratory tests
- Sampling for PK (week 2 only)
- ECG (weeks 4 and 8 only)
- Adverse events
- Serum pregnancy test
- Sampling for PK

13.1.4 Interventions

Treatment with istradefylline 40 mg/day or matching placebo

The Sponsor's Presentation of Their Rational for Determining Sample Size

The sample sizes of the treatment groups were based on the expected difference between treatment groups in the percentage of time OFF from Baseline to Endpoint for the ITT population. A total of 120 subjects in the istradefylline group were planned to be randomized to obtain at least 100 subjects in the ITT population. For the placebo group, 60 subjects were planned to obtain at least 50 subjects in the ITT population. The sample size of each treatment group was sufficient to provide 80% power to detect statistical significance at the 2-sided alpha level of 0.050 for treatment group differences greater than or equal to 50% of the applicable

standard deviation. The actual numbers of subjects analyzed in the primary analysis were 129 and 66 subjects, respectively.

13.1.5 Randomization

Subjects meeting screening criteria were randomly assigned to receive istradefylline 40 mg/day or placebo in a 2:1 ratio favoring istradefylline. Randomization took place during the baseline (day -1) visit according to a schedule created by Kyowa.

13.1.5.1 Blinding

Subjects, study site personal and the sponsor were to remain blinded to treatment assignment until completion of the study, data validation and database lock. The sponsor did not report any instance where the study blind was compromised.

14 STATISTICAL METHODS

14.1 Data Analysis Plan

The primary efficacy analyses will be carried out based on the intent-to-treat (ITT) patient population. The ITT population is defined as patients who consume at least one dose of study drug and provide at least one patient diary with "ON/OFF" assessments. The last observation carried forward (LOCF) approach will be used to define the Endpoint for each of the efficacy variables.

The initial statistical analysis plan described in the original protocol was a 2-way ANCOVA with adjustment terms for investigator, treatment and the interaction term treatment by investigator. The final statistical analysis plan of the (SAP) called for a 2-way ANOVA with terms for the investigator and treatment. The SAP was finalized prior to unblinding on May 2, 2003 with an addendum submitted on June 20, 2003 included in the addendum was the statement informing the division that the 2-way ANOVA model would be used for analysis of the applicable endpoints.

Data Analysis Per The Sponsor's Study Report

All efficacy variables (except CGI-I) were analyzed using a 2-way analysis of variance (ANOVA). For the primary efficacy variable, a model with terms for Investigator, treatment, and treatment-by-investigator interaction was initially fitted and the interaction effect was tested at the 2-sided alpha level of 0.150. The interaction term was found to be not statistically significant (p-value = 0.336; Appendix 16.1.9.1, Table 16.1.9.1) and the main effect model was

accepted for the primary analysis. The normality assumption of the ANOVA model for the primary efficacy variable was tested using Shapiro-Wilk test for the residual for the ANOVA model at the alpha level of 0.050. The test for normality was found to be not statistically significant (p-value = 0.544) further supporting the usage of the main effects model (see Appendix 16.1.9.1, Table 16.1.9.25). For all secondary efficacy variables, only the main effects ANOVA model with terms for Investigator and treatment were used. No testing for treatment-by-investigator interaction or testing for the normality assumption was carried out for the secondary efficacy variables.

The CGI-I variable was analyzed using a Cochran-Mantel-Haenszel (CMH)20 with row mean scores test using modified scores and stratifying by Investigator.

Handling and Analysis of Missing Data

The last observation carried forward (LOCF) approach was used to define the endpoint for each of the efficacy variables.

Primary Efficacy Variable

The sponsor analyzed subject diary data using two methods to adjust for missing and invalid diary entries.

Observed case Analysis

Valid subject diaries had < 2 hours of missing or invalid entries all valid entries were entered into the database. All missing data or invalid time points in an otherwise valid 24-hour diary were excluded from the observed case analysis.

Worst Case Analysis

All missing time points in an otherwise valid 24-hour diary were imputed as "OFF". All invalid time (multiple entries) were imputed according to the rank orders system to the worst case value.

The order defining the worst case value was as follows (in declining order from best to worst): asleep < ON without dyskinesia < ON with non-troublesome dyskinesia < ON with troublesome dyskinesia < OFF.

Reviewer Comment

The method of handling missing diary entries is rational but the opportunity to have the study coordinator or investigator review the diary and query subject in person about double entries may be a better approach.

Recruitment

Subjects were recruited by site investigators from their individual clinic populations.

Table 3.1 (Kyowa Table)

STUDY FLOWCHART

6002-US-005	Initial Visit+	Baseline	Double Blind Treatment End of Week (+/- 4 Days)*			
Assessment	**Week -2**	**Day -1#**	**2**	**4**	**8**	**12/ ET**
Written informed consent	X					
Inclusion/Exclusion Criteria	X					
Medical history	X					
Physical/Neurological Exam**	X					X
Brief Physical Exam		X				
Height	X					
Weight	X	X				X
Vital signs (sitting)^	X	X	X	X	X	X
Laboratory tests	X	X	X	X	X	X
Sampling for PK			X			X
Serum Pregnancy Test%%		X				X
ECG	X	X		X	X	X
MMSE	X					
Conduct Diary training	X					
Patient Diary Review		X#	X	X	X	X
Final eligibility assessment and randomization		X				
UPDRS Subscales I, II, III~, IVA, IVB, IVC		X	X	X	X	X
Clinical Global Impression Severity of Illness		X				
Clinical Global Impression Global Improvement			X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Adverse Events		X	X	X	X	X
Dispense Drug		X	X	X	X	
Dispense Diary	X	X	X	X	X	

ET = Early Termination

Patients with more than 4 invalid entries in any one of their two daily diaries must repeat the Baseline (Day-1) visit seven days later. Patients failing the validity criterion for a second time are precluded from participating in the trial.

+ The initial visit will occur approximately two weeks prior to Day –1 (or up to eight weeks if taper from prohibited medication is required) to ensure patients meet 'OFF' time criteria through diary completion.

* It is important to maintain the visit structure as accurately as possible. In the rare case in which an adjustment to this structure is necessary, the visit should occur within 4 days of the planned schedule. The timing of subsequent visits should be planned to maintain the visit structure relative to the first day double-blind medication was taken.

** Neurological exam is to be performed during the same state (either 'ON' or 'OFF') at both the Week –2 and Week 12/ET visits.

^ Vitals are to be conducted during the 'ON' state.

~ UPDRS III to be conducted in the "ON" and "OFF" states at Day –1, Week 4 and 12 and only in the "ON" state at Weeks 2 and 8.

%% Women of childbearing potential.

15 PATIENT DEMOGRAPHICS

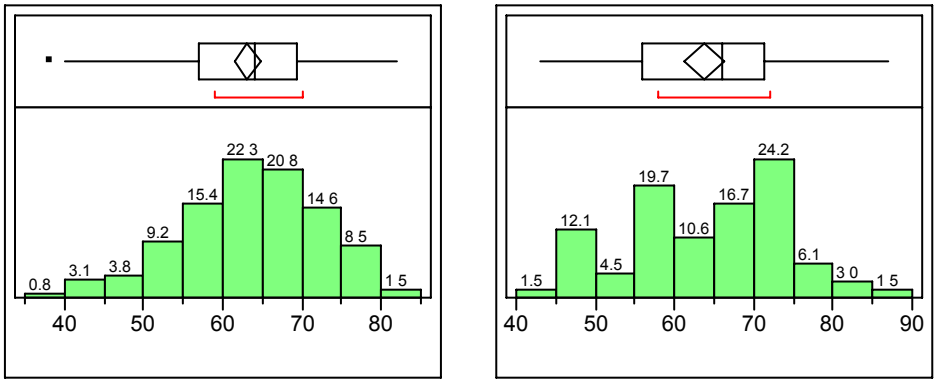
The subject base characteristics did not reveal significant differenced between the istradefylline and placebo treated groups. The median age of subjects in the placebo group was 2 years greater even though the mean age was similar. Review baseline characteristics found the placebo group has a greater percentage of subjects older than 70 (34.8% vs 24.6%) compared to the istradefylline 40 mg/day group. Also the placebo group had a higher percentage of patients who were rated as having a greater severity of illness (CGI-S) at baseline. 18.1% of subjects in the placebo group had a CGI-S scale score of "Markedly, Severely or Among the most extremely ill" at baseline compared to the istradefylline group that only had 11.6% of the subjects in the same severity of illness categories. Neither of these small difference in age or disease severity at baseline appeared to influence the between group difference. The sponsor's regression model found no evidence of a relationship between age or severity of illness (CGI-S) at baseline and the change in percent of awake off time.

Table 4.1 The Sponsor's Representation of Demographic and Other Baseline Study 6002-US-005

Characteristics (Intent-to-treat Population)			
		Istradefylline	
	Placebo	**40 mg/day**	**Total**
Demographic Characteristic	**(N=66)**	**(N=129)**	**(N=195)**
Age (years)			
Mean	63.7	63	63.2
SD	10.06	8.98	9.34
Median	66	64	64
Range (min-max)	43 to 87	38 to 80	38 to 87
Sex (n [%])			
Male	40 (60.6)	77 (59.7)	117 (60.0)
Female	26 (39.4)	52 (40.3)	78 (40.0)
Race (n [%])			
Caucasian	61 (92.4)	124 (96.1)	185 (94.9)
Black	2 (3.0)	1 (0.8)	3 (1.5)
Asian	1 (1.5)	1 (0.8)	2 (1.0)
Hispanic	1 (1.5)	1 (0.8)	2 (1.0)
Other	1 (1.5)	2 (1.6)	3 (1.5)

Table 4.2

KW-6002 40 mg/day AGE **Placebo AGE**



Reviewer Comment

The difference in the distribution of age shifted slightly to the 70-80 year bracket in the placebo group is unlikely to affect the efficacy profile or AE profile of istradefylline. The placebo group may experience a greater number of AEs in general because of a slightly mean age but small difference in mean age is unlikely to cause a significant difference.

Table 4.3 The Sponsor's Representation of Parkinson's Disease History at Baseline Study 6002-US-005 (Adapted From Kyowa Table)

Parkinson's Disease History at Baseline	(Intent-to-treat Population)		
		Istradefylline	
	Placebo	40 mg/day	Total
	(N=66)	(N=129)	(N=195)
Time since diagnosis (years)			
n[a]	44	75	119
Mean	9.27	9.3	9.29
SD	5.122	4.685	4.83
Median	7.95	8.5	8.4
Range (min to max)	1.4 to 19.1	2.4 to 25.6	1.4 to 25.6
Time since onset of motor complications (years)			
n[a]	44	77	121
Mean	3.57	3.29	3.39
SD	3.203	2.511	2.773
Median	2.35	2.7	2.5
Range (min to max)	0.2 to 15.2	0.1 to 11.9	0.1 to 15.2

Note: Duration of PD history was calculated relative to the screening visit date.
[a] Included only subjects who had no missing value for both the month and year of the event time.
SD = standard deviation; min = minimum; max = maximum

The duration of PD or motor complications was similar between the two treatment groups. The placebo group had a slightly greater percentage of subjects who were rated as markedly Ill on the CGI_I scale, but this did not appear to be a meaningful difference.

Table 4.4 (Kyowa Table)

Table 11.2.2-5 Parkinson's Disease Characteristics at Baseline: Clinical Global Impression-Severity of Illness Scores (Intent-to-treat Population)

Characteristic	Placebo (N=66) n (%)	Istradefylline 40 mg/day (N=129) n (%)	Total (N=195) n (%)
Borderline ill	6 (9.1)	11 (8.5)	17 (8.7)
Mildly ill	12 (18.2)	23 (17.8)	35 (17.9)
Moderately ill	36 (54.5)	79 (61.2)	115 (59.0)
Markedly ill	9 (13.6)	12 (9.3)	21 (10.8)
Severely ill	2 (3)	3 (2.3)	5 (2.6)
Among the most extremely ill	1 (1.5)	0 (0.0)	1 (0.5)
Missing	0 (0.0)	1 (0.8)	1 (0.5)

Table 4.5 (Kyowa Table)

Table 10.1-1 Subject Disposition

Status	Placebo (N=66) n (%)	Istradefylline 40 mg/day (N=130) n (%)
All Subjects Randomized	66 (100.0)	130 (100.0)[a]
Safety Population[b]	66 (100.0)	129 (99.2)
Intent-to-Treat Population[c]	66 (100.0)	129 (99.2)
Completed		
Week 2	64 (97.0)	126 (96.9)
Week 4	59 (89.4)	120 (92.3)
Week 8	58 (87.9)	117 (90.0)
Completed Double-blind Treatment Period	58 (87.9)	114 (87.7)
Discontinued Study Prematurely	8 (12.1)	16 (12.3)
Reason for Discontinuation from Study		
Lack of efficacy	0 (0.0)	1 (0.8)
Adverse events	5 (7.6)	10 (7.7)
Protocol violation or non-compliance with study drug	0 (0.0)	1 (0.8)
Subject withdrew consent	3 (4.5)	4 (3.1)

[a] Subject No. (b) (6) experienced adverse events prior to receiving study drug and was discontinued from the study. This subject was not included in any efficacy or safety analyses.
[b] All randomized subjects who received at least 1 dose of study drug.
[c] All randomized subjects who received at least 1 dose of study drug and had a Baseline and at least 1 post-baseline efficacy measurement.
Source: End-of-Text Table 14.1.2 and Appendix 16.2, Listing 16.2.2

16 ANALYSIS OF EFFICACY

16.1 Primary Outcome Variable

Table 5.1-Change in % of Daily Awake OFF Time

Change from Baseline at Endpoint			
.	65	126	
Mean	-4	-10.81	p=0.007
SD	15.743	16.556	
Median	-4.2	-10.55	
Min to max	-49.1 to 25.6	-50.4 to 47.5	

16.2 Secondary Outcome Variables

Table 5.2 (Kyowa Table)

Table 11.4.1-3 Change From Baseline to Endpoint in Total Hours of Awake Time Per Day Spent in an OFF State (Intent-to-treat Population)

	Total Hours of Awake Time Per Day Spent in an OFF State[a]		
Visit	Placebo (N=66)	Istradefylline 40 mg/day (N=129)	p-value[b]
Baseline			
n	66	129	
Mean	6.20	6.37	
SD	2.457	2.724	
Median	5.80	6.0	
Min to max	2.0 to 12.3	0.0 to14.5	
Endpoint			
n	65	126	
Mean	5.49	4.55	
SD	2.839	2.803	
Median	5.80	4.30	
Min to max	0.0 to 10.3	0.0 to 13.8	
Change from Baseline at Endpoint			
n	65	126	
Mean	-0.64	-1.79	0.006
SD	2.733	2.764	
Median	-0.70	-1.70	
Min to max	-7.0 to 4.8	-8.8 to 5.5	

[a] Based on subjects' valid ON/ OFF PD diary data from observed-case analysis.
[b] The p-value based on least squares mean from 2-way ANOVA, including terms for Investigator and treatment.
SD = standard deviation; min = minimum; max = maximum

Change From Baseline in Percentage of Awake Time Per Day Spent in an OFF State by Study Visit

Comparisons were made from baseline percent of awake OFF time to weeks 2,4,8,12 (endpoint) all of the between group differences by study visit were statistically significant with the exception of the week 4 visit which was nearly significant at p=0.06.

Change From Baseline in Total Hours of Awake Time Per Day Spent in an OFF State by Study Visit

The difference in total daily hours spent on the OFF state from baseline broken down by study visit again revealed a statistically significant difference for all visits except week 4. In this case the trend was closer to the pre-determined alpha, p=0.075.

Table 5.3-ON State Without Dyskinesia

Percentage of Awake Time Per Day in an ON state Without Dyskinesia			
	Placebo	Istradefylline 40 mg/day	
n	65	126	
Mean	7.06	8.03	p=0.655
SD	18.711	18.933	
Total Hours of Awake Time Per Day in an ON state Without Dyskinesia			
n	65	126	
Mean	1.07	1.24	p=0.617
SD	2.888	3.136	

Reviewer Comment

The sponsor's rational included the possibility that istradefylline may improve the motor symptoms of PD without worsening dyskinesia. This analysis suggests istradefylline increase the duration of dyskinesia compared to placebo.

Change From Baseline in Percentage of Awake Time Per Day in an ON State Without Dyskinesia by Study Visit (Intent-to-treat Population)

The difference between istradefylline 40 mg/day and the placebo group in the mean percent of the awake day spent with dyskinesia was not statistically significant. The mean percentage of time spent with dyskinesia was numerically greater in the istradefylline group with the exception of the week 8 visit.

Change From Baseline in Total Hours of Awake Time Per Day Spent in an ON State Without Dyskinesia by Study Visit (Intent-to-treat Population)

The difference between istradefylline 40 mg/day and the placebo group in the mean total hours of the awake day spent with dyskinesia was not statistically significant. The mean total hours of ON time with dyskinesia was numerically greater in the istradefylline group with the exception of the week 8 visit.

Table 5.4-Awake Time Spent ON with Dyskinesia

Change from Baseline at Endpoint			
	Placebo	**Istradefylline 40 mg/day**	**p value**
Percentage of Awake Time Per Day Spent in an ON state With Dyskinesia			
n	65	126	
Mean	-3.02	2.78	0.047
SD	14.61	19.809	
Total hours of Awake Time Per Day Spent in an ON state With Dyskinesia			
n	65	126	
Mean	-0.5	0.5	0.035
SD	2.379	3.224	

The percent and total hours spent in the ON state with dyskinesia is significantly greater in the istradefylline group compared to the placebo group. Similar results are found in the analysis of ON time spent with dyskinesia expressed as a percent or in total hours by visit with the exception of the percent of awake on time with dyskinesia at week 4 (p=0.098).

Change From Baseline at Endpoint in Percentage and Hours of Awake Time Per Day Spent in an ON State With Non-troublesome Dyskinesia (Intent-to-treat Population)

The difference from baseline to endpoint, for the percent and total hours of daily awake ON time spent with Non-troublesome dyskinesia was numerically greater in the istradefylline group, but it was not statistically significant compared to placebo.

Change From Baseline at Endpoint in Percentage and Hours of Awake Time Per Day Spent in an ON State With Non-troublesome Dyskinesia By Visit (Intent-to-treat Population).

The between group difference was statistically significant for weeks 2, 4, 8, but not for week 12 (completion endpoint) for both the percent and total hours spent in the ON state with Non-troublesome dyskinesia.

Table 5.5
Change From Baseline to Endpoint in Percentage and Total Hours of Awake Time Per Day Spent in an ON State With Troublesome Dyskinesia (Intent-to-treat Population) (Adapted from Kyowa Table)

Percent Chang Spent in an ON State With Troublesome Dyskinesia			
	Placebo	**Istradefylline 40 mg/day**	**p=value**
n	65	126	
Mean	0.42	1.58	0.408
SD	8.139	9.611	
Total Hours Spent in an ON State With Troublesome Dyskinesia			
n	65	126	
Mean	0.08	0.3	0.347
SD	1.384	1.573	

The percent and hours spent in the ON state with troublesome dyskinesia from baseline to endpoint are numerically greater but they are not statistically significant.

Change From Baseline in Percentage and Total Hours of Awake Time Per Day Spent in an ON State With Troublesome Dyskinesia by Study Visit (Intent-to-treat Population)

At the week 2 visit both the percent change and total hours of awake hours spent in the ON state with troublesome dyskinesia compared to baseline were greater in the istradefylline treated groups compared to placebo. The between group difference was statistically significant for both secondary outcome variables, the p value for the percent change was p=0.028 and for total hours the p value=0.013 indicating troublesome dyskinesia was significantly worse at visit 2 in the istradefylline treated group. Data from visits week 4, 8, and 12 (endpoint) the between group differences were not statistically significant for either percent change from baseline or change in total hours.

On State Without Troublesome Dyskinesia

The sponsor indicated at the bottom of the study report synopsis the variable "On state without troublesome dyskinesia" is a derived variable created post-hoc, after unblinding of the study database. Since the treatment blind was broken before the analysis of this variable, it will not be considered as part of the efficacy review. The sponsor's analysis of the ON state without troublesome dyskinesia indicates the change in percent and total hours from baseline to endpoint and from baseline to each scheduled visit all favored istradefylline over placebo, with statistically significant between group differences.

The Sponsor's Statement

"In addition, the analysis of ON state without troublesome dyskinesia, defined as the sum of ON state without dyskinesia and ON state with non-troublesome dyskinesia, were added after the unblinding of treatment codes."

Reviewer's Comment

The sponsor stated in the study report: "The final SAP was signed on 2 May 2003 with an addendum added on 20 June 2003. The database was locked on 23 June 2003, and data were unblinded for the efficacy analyses on 26 June 2003." The sponsor's post hoc, unblinded, analysis of "ON state without troublesome dyskinesia" was excluded from the efficacy review because the analysis fails to protect against a type I error and it is likely to result in false conclusions of a positive outcome.

Table 5.6 (Kyowa Table)
Unified Parkinson's Disease Rating Scale (UPDRS)

Table 11.4.1-20 Change From Baseline at Endpoint in UPDRS I-IV Total Score (Intent-to-treat Population)

	UPDRS I-IV Total Score[a]		
	Placebo (N=66)	Istradefylline 40 mg/day (N=129)	p-value[b]
Baseline			
n	59	120	
Mean	32.4	31.7	
SD	17.06	15.37	
Endpoint			
n	66	129	
Mean	30.9	28.8	
SD	19.02	16.86	
Change from Baseline at Endpoint			
n	59	120	
Mean	-1.5	-2.0	0.598
SD	9.97	8.42	

[a] UPDRS I-IV total score = the sum of UPDRS Questions 1 to 42, including ON time rating for UPDRS subscale II and UPDRS subscale III; Question 36 was recorded as 1=No and 2=Yes. A lower score indicates a more favorable response.
[b] The p-value based on least squares mean from 2-way ANOVA, including terms for Investigator and treatment.
SD = standard deviation

Analysis of the UPDRS total score (parts I-IV) in the ON state, for the change from baseline to endpoint did not find a statistically significant difference between the placebo and istradefylline treated groups. A comparison of the total UPDRS scores from baseline to scores at each scheduled visit found a statistically significant difference at the week 8 visit only

Table 5.7 (Kyowa Table)

Table 11.4.1-22 Change From Baseline at Endpoint in UPDRS Subscale III Total Score in ON and OFF State (Intent-to-treat Population)

	Placebo (N=66)	Istradefylline 40 mg/day (N=129)	p-value[a]
UPDRS Subscale III Total Score[b] in the ON State			
Baseline			
n	60	122	
Mean	18.0	17.7	
SD	11.17	11.09	
Endpoint			
n	66	129	
Mean	17.7	16.8	
SD	12.58	12.56	
Change from Baseline at Endpoint			
n	60	122	
Mean	-0.2	-0.4	0.822
SD	7.43	7.40	
UPDRS Subscale III Total Score[b] in the OFF State			
Baseline			
n	58	121	
Mean	38.4	35.4	
SD	13.62	13.39	
Endpoint			
n	60	121	
Mean	35.1	32.5	
SD	13.12	13.05	
Change from Baseline at Endpoint			
n	53	113	
Mean	-2.9	-2.8	0.838
SD	8.87	8.56	

[a] The p-value based on least squares mean from 2-way ANOVA, including terms for Investigator and treatment.
[b] UPDRS subscale III total scale = Sum of UPDRS Questions 18 to 31 (Motor Examination). A lower score indicates a more favorable response.
SD = standard deviation
Source: End-of-Text Tables 14.2.9.1.1, 14.2.9.1.2, 14.2.9.2.1, and 14.2.9.2.2

The change in the UPDRS part III (motor exam) scores from baseline to endpoint did not find a statistically significant difference between the placebo and istradefylline treated groups in the ON or OFF states. Part II or the activities of daily living section of the UPDRS also failed to demonstrate a statistically significant difference between the placebo and istradefylline treated groups (see M 5.3.5.1.3, Table 14.2.8.1).

Reviewer Comment

The UPDRS total score and its' subscale scores often serve as the primary endpoint in pivotal trials for medications seeking approval for the treatment of the motor symptoms of PD. The motor subscale (part III) is an evaluation performed by a neurologist who trained in administering and scoring the UPDRS. **The failure of istradefylline to demonstrate a significant improvement in the total UPDRS score or one of its' key subscales scores (part III), suggests it has a small effect in improving the motor symptoms of PD.**

Table 5.7 (Kyowa Table)

Table 11.4.1-23 Clinical Global Impression - Improvement at Endpoint (Intent-to-treat Population)

Score	Placebo (N=66) n (%)	Istradefylline 40 mg/day (N=129) n (%)	p-value[a]
Endpoint[b]			0.326
Very much improved (1)	1 (1.5)	3 (2.3)	
Much improved (2)	13 (19.7)	30 (23.3)	
Minimally improved (3)	13 (19.7)	36 (27.9)	
No change (4)	32 (48.5)	42 (32.6)	
Minimally worse (5)	5 (7.6)	16 (12.4)	
Much worse (6)	2 (3.0)	2 (1.6)	

[a] The p-value is based on Cochran-Mantel-Haenszel row mean score test using modified scores.
[b] No subject was reported as having symptoms of Parkinson's disease scored as very much worse (7) compared with the subject's condition at Day -1.
Source: End-of-Text Table 14.2.10

The Clinical Global Impression–Improvement scores also did not demonstrate a statically difference from baseline to endpoint in the istradefylline group compared to placebo. The CGI-I score is often selected as a co-primary endpoint in chronic diseases where an acceptable external marker (biomarker) is not feasible.

Reviewer Comment

The CGI-I is another traditionally important endpoint that fails to demonstrate a significant improvement in scores in the istradefylline treated group compared to the placebo group. The failure of istradefylline to demonstrate superiority compared to placebo on the global measure of improvement suggest the effects of istradefylline 40 mg/day is not clinically meaningful.

17 EFFICACY CONCLUSIONS FOR STUDY 6002-US-005

Subjects receiving istradefylline 40 mg/day demonstrates statistically significant improvement over placebo for the primary efficacy endpoint (percent change in daily awake time spent in the OFF state). Secondary endpoints closely related to the primary endpoint such as total off hours also demonstrate a significant difference between the treatment groups. Other outcome measures (UPDRS, CGI-I) that are unrelated to the primary outcome measure do not demonstrate superiority of istradefylline over placebo. The UPDRS incorporates subscales that convey information concerning change in function such as activities of daily living and motor performance. Istradefylline seems to reduce time spent in the OFF state for just over one hour for the subject's awake part of the day, without improving motor function or performance of ADLs. The 6002-US-005 study demonstrated the strongest association of istradefylline with a change in the primary outcome variable of all the pivotal trials included in the sponsor's application.

18 SAFETY REVIEW

Analysis of the integrated review of safety (ISS) included data from the 6002-US-005 study in the analysis of the safety data in pools I and V.

18.1 Exposure

Table 7.1 Exposure (Kyowa Table)

Table 12.1-1 Duration of Double-blind Treatment (Safety Population)

Duration (weeks) on Study Drug[a]	Placebo (N=66)	Istradefylline 40 mg/day (N=129[b])
By interval (n [%])		
≤ 2	1 (2)	3 (2)
> 2 to ≤ 5	7 (11)	9 (7)
> 5 to ≤ 9	0	1 (<1)
> 9 to ≤ 13	55 (83)	112 (87)
> 13	3 (5)	4 (3)
Summary statistics		
Mean	11.07	11.16
SD	2.863	2.845
Median	12.00	12.00
Range (min to max)	1.9 to 13.9	0.3 to 14.3

[a] Duration = ([last dose date−first dose date] + 1)/7.
[b] Does not include Subject No. (b) (6) who was randomized but did not receive study drug.
SD = standard deviation; min = minimum; max = maximum

The trial was scheduled for 12 weeks; dropouts from the trial did not significantly affect the mean duration of exposure.

18.2 Patient Disposition

Table 7.2 (Kyowa Table)

Table 10.1-1 Subject Disposition

Status	Placebo (N=66) n (%)	Istradefylline 40 mg/day (N=130) n (%)
All Subjects Randomized	66 (100.0)	130 (100.0)[a]
Safety Population[b]	66 (100.0)	129 (99.2)
Intent-to-Treat Population[c]	66 (100.0)	129 (99.2)
Completed		
Week 2	64 (97.0)	126 (96.9)
Week 4	59 (89.4)	120 (92.3)
Week 8	58 (87.9)	117 (90.0)
Completed Double-blind Treatment Period	58 (87.9)	114 (87.7)
Discontinued Study Prematurely	8 (12.1)	16 (12.3)
Reason for Discontinuation from Study		
Lack of efficacy	0 (0.0)	1 (0.8)
Adverse events	5 (7.6)	10 (7.7)
Protocol violation or non-compliance with study drug	0 (0.0)	1 (0.8)
Subject withdrew consent	3 (4.5)	4 (3.1)

[a] Subject No. (b) (6) experienced adverse events prior to receiving study drug and was discontinued from the study. This subject was not included in any efficacy or safety analyses.
[b] All randomized subjects who received at least 1 dose of study drug.
[c] All randomized subjects who received at least 1 dose of study drug and had a Baseline and at least 1 post-baseline efficacy measurement.

The percent of subjects who dropped out from the trial prematurely was similar in both treatment groups. The percent of subjects who dropped out of the trial prematurely due to adverse event was also similar.

Table 7.1 Adverse Events Leading to Dropout Istradefylline 40 mg –Preferred Terms

Excessive sleepiness	Worsening asthma
Lack of efficacy	Worsening PD
Chest pain	Nausea/rigidity/tremor
Weakness	Severe motor fluctuations
Hip fracture	Nausea/dizziness/headache

18.2.1 Deaths

The narratives for each case of death in the 6002-US-005 study were reviewed and are contained in the ISS section of the review. A brief summary of the 2 death that occurred on istradefylline 40 mg and a single death in a subject on placebo is presented here.

Istradefylline 40 mg/day

Subject (b) (6). The subject was a 64 year-old Caucasian man with a significant medical history of asthma and basal ganglia lacunar infarction. He received 40 mg of istradefylline in a blinded fashion and during a schedule visit (day 66) he reported emesis for the 4 day preceding the visit without reporting associated symptoms. He self medicated his symptoms with Emetrol, Advil and Pepto-Bismol. Five days later (day 71) the subject was contacted by phone and he reported persistent vomiting again without other complaints. He was instructed to discontinue study drug and he was seen in clinic for an unscheduled visit with clinical lab testing. The sponsor's description of the lab results from the unscheduled visit was "slightly abnormal" for WBCs, platelets, neutrophil, alkaline phosphatase, trypsin-like immunoreactivity, amylase, lipase and glucose. Attempts to contact the subject by phone were unsuccessful on days 80 and 84. The subject was found deceased in his home by local law enforcement. The estimated time of his demise was 7-10 days prior to discovery by the Sherriff. The death was listed as "unattended", the investigator considered the death unrelated to study drug and classified the death as related to worsening asthma. The subject had an elevated total bilirubin, trypsin-like immunoreactivity, lipase and amylase at the week 8 (scheduled visit) which increased at the time of the unscheduled visit with only lipase elevated to > 3X ULN. The BUN remained with in the normal range at the week 8 and unscheduled visits 6.1 mmol/L and 5.5 mmol/L respectively (nl=1.4-8.6 mmol/L for males age 18-69). SGOT, SGPT and Bilirubin remained with in the normal range. The cause of death was coded inappropriately as related to asthma, although the reviewer suspects the subject had **pancreatitis** prior to his demise the actual cause of death remains unknown.

Subject (b) (6) The subject was a 67 year-old Caucasian man who received 40 mg of istradefylline per day. His relevant past medical history includes gastritis, urinary incontinence

and erectile dysfunction. The subject discontinued study medication on day 17 because dyskinesia. On day 24 he suffered a cardiac arrest at home and attempts to resuscitate him were unsuccessful.

Placebo

Subject (b) (6) The subject was a 71 year-old female the sponsor listed her cause of death as "accident NOS, skull fracture NOS, and pneumonia NOS". Her past medical history included mild COPD, lung surgery for bronchiectasis, bipolar disorder, osteoporosis, mandibular setback, and right total knee arthroplasty. The subject fell down steps in her home on study day 27 resulting in "frontal lobe bruising without hemorrhage" on CT scan. The subject became progressively more sedate and eventually she became comatose. The subject developed pneumonia on day 31 and died the next day.

18.3 Serious Adverse Events

Table 7.3 (Kyowa Table)
The Sponsor's Listing of Serious Adverse Events By Preferred Term

Table 12.3.1-1 Subjects Who Experienced Serious Adverse Events (Safety Population)

Center/ Subject	Sex/Age/ Race[a]	Onset Day[b]	End Day[b]	Adverse Events (Preferred Term)[c]	Severity	Relationship
Treatment-Emergent Serious Adverse Events						
Placebo						
(b) (6)	F/71/C	31	32	Pneumonia NOS[d]	Severe	Not Related
		27	32	Skull fracture NOS	Severe	Not Related
		27	27	Accident NOS	Severe	Not Related
Istradefylline 40 mg/day						
	F/63/C	14	17	Abdominal pain NOS	Severe	Not Related
		14	17	Abdominal distension	Severe	Not Related
	F/68/C	17	18	Chest pain	Moderate	Not Related
	F/72/C	64	100	Confusional state	Severe	Not Related
	M/60/C	39	42	Ileus paralytic	Severe	Not Related
	M/64/C	73	73	Asthma aggravated[d]	Severe	Not Related
	M/55/C	54	57	Chest pain	Severe	Not Related
	M/70/C	5	12	Asthenia	Severe	Not Related
	M/67/C	23	24	Cardio-respiratory arrest[d]	Severe	Not Related
	M/69/C	64	115	Parkinsonism aggravated	Moderate	Possibly
	F/75/C	108	111	Skin graft NOS	Severe	Not Related
Not Treatment-Emergent Serious Adverse Events						
Placebo						
	F/66/C	-14	-13	Goitre	Severe	Not Related
Istradefylline 40 mg/day						
	F/82/C	-1[e]	98[e]	Hip Fracture	Severe	Not Related
		-1[e]	-1[e]	Accident NOS	Moderate	Not Related

A total of 13 subjects reported 17 serious adverse events (SAE). Chest pain and fall were the only reported SAEs to have occurred more than once. Regrouping SAE PTs to higher level, higher level group terms and system organ class did not yield additional information because of the small number of SAEs reported during the trial. There were no cases of rare or index events to suggest an increased event rate over the background of a particular SAE. There were no cases

of hepatic failure, aplastic anemia, neutropenia, Stevens-Johnson Syndrome or new acute renal failure.

Vital signs

There were no significant, istradefylline associated individual subject reports or mean group difference in heart rate reported during this trial. Orthostatic changes in pulse and blood pressure (BP) was not monitored during this trial but they were monitored in the 6002-US-006 trial. Review of the data regarding orthostatic changes in vital signs from the 6002-US-006 study in included in the ISS section of in this review. The mean systolic and diastolic changes in BP were similar for the istradefylline and placebo treated groups. One subject in both the placebo and the istradefylline treated groups experienced a decline in diastolic BP that was clinically significant (decline ≥ 15 mmHg or value < 50 mmHg). The subject in the placebo group developed Wolff-Parkinson-White Syndrome associated with the decline in diastolic BP. The subject in the istradefylline group had an episode of a decline in BP (111/45 mmHg) associated with chest pain. The subject's BP taken during previous study visits indicated systolic hypertension at baseline. Two subjects in each group developed significant systolic hypertension during the trial. Subject (b) (6) received istradefylline 40 mg/day, entered the trial with a BP =142/70 which increased to 184/80 mm Hg by week 2 and it remained elevated through out the completion of the trial 177/72 mm Hg at week 12). There were no reported instances of significant diastolic hypertension (>105 mmHg and an increase of ≥ 15 mmHg).

Overall, the data did not indicate a safety concern for istradefylline 40 mg with regards to pulse or blood pressure on the 6002-US-005 study.

18.4 Clinical Lab Values

Hematology

There were no significant differences for changes in the mean values of hematological or chemistry lab values comparing baseline to endpoint or baseline to individual study visit. There were 5 cases of neutropenia that were < 3.9 WBC x 10^9/L, in all 5 cases there baseline and screening visit values were also low. In all but one case the WBC remained stable through the course of the trial. In the subject were the WBC decreased (1.25 to 0.84) the values were stable until week 12 (the final visit), given the low WBC of 1.25 at the screening visit this subject should have been excluded from trial participation at baseline. There were no cases of treatment emergent neutropenia, aplastic anemia or serious thrombocytopenia reported during the trial.

Table 7.4 (Kyowa Table)

Table 12.4.2-2 Subjects With Laboratory Adverse Events: Blood Alkaline Phosphatase NOS Increased and Corresponding ALT, AST and LDH Values (Safety Population)

Center/ Subject	Laboratory Variable (U/L)	Reference Range (U/L)	Study Visit					
			Week -2	Day -1	Week 2	Week 4	Week 8	Week 12
			Istradefylline 40 mg/day					
(b) (6)	Alkaline Phosphatase	35 to 130	114	111	118	138 H	123	**158 H[a]**
	ALT	6 to 35	20	13	13	17	16	23
	AST	11 to 36	24	26	19	26	23	27
	LDH	53 to 234	188	200	192	200	188	238 H
	Alkaline Phosphatase	35 to 123	97	109	94	108	105	**133 H[a]**
	ALT	6 to 34	5	8	7	7	4 L	11
	AST	9 to 34	11	NA	13	14	14	12
	LDH	53 to 234	169	NA	190	196	188	188
	Alkaline Phosphatase	35 to 125	87	87	83	95	**158 H[a]**	NA 127 H (62)[b]
	ALT	6 to 43	6	18	12	23	48 H	NA 35 (62)[b]
	AST	11 to 36	14	16	13	19	73 H	NA 22 (62)[b]
	LDH	53 to 234	160	159	154	159	195	NA 167 (62)[b]
	Alkaline Phosphatase	35 to 135	*162 H*[c]	*166 H*[c]	**185 H[a]**	169 H	176 H	178 H
	ALT	6 to 32	22	31	35 H	24	29	43 H
	AST	9 to 34	28	34	29	28	43 H	34
	LDH	53 to 234	150	153	161	140	161	135

[a] Alkaline phosphatase increases that were considered adverse events.
[b] Unscheduled visit (Day of unscheduled visit).
[c] Alkaline phosphatase value above the upper limit of the reference range prior to receiving study drug.
ALT = alanine transferase; AST = aspartate transferase; H = above the upper limit of the reference range; L = below the lower limit of the reference range; LDH = lactate dehydrogenase; NA = not available; NOS = not otherwise specified
Source: Appendix 16.2, Preface to Listing 16.2.12.1 and Listing 16.2.12.1

Chemistry

Liver Enzymes

No subjects met criteria for Hy's Law (ALT or AST ≥ 3 X ULN with total bilirubin ≥ 1.5 X ULN). Only a single individual that had liver enzymes (ALT) approaching 3 X ULN measured at the baseline visit and at week 8. The AST and ALT were mildly elevated at the baseline visit, the ALT increased greater than the AST that remained at a mildly elevated level (1.3 X ULN). There were no cases of hepatic failure reported during the trial. Mean changes in ALT and AST by study visit or from baseline to endpoint did not indicate a significant change in liver enzymes.

Four subjects who received istradefylline 40 mg/day had elevated alkaline phosphatase levels during the course of the trial. One subject had elevated levels at baseline but in all 4 subjects the levels remained higher than baseline over the course of the trial. In 2 subjects the elevation in alkaline phosphatase was accompanied by mild elevations of ALT and/or AST. One subject has a mildly elevated LDH as an isolated event in week 12 (endpoint).

Amylase and Lipase

The percent of subjects who experienced an increase in amylase or lipase was greater in the placebo group. Subject ((b) (6)) received 40 mg istradefylline/day experience a sudden elevation of amylase, lipase and trypsin-like immunoreactivity just prior to his unattended death. The cause of death was not attributed to pancreatitis but it cannot be excluded as a contributing factor. The mean group and individual subject change values for lipase, amylase and Trypsin like immunoreactivity did not indicate increasing values over the course of the trial.

Chemistry and Glucose

Glucose, BUN and Triglycerides were the most frequently encountered abnormal lab values. Hypoglycemia (glucose < 3.0 mmol/L occurred in 4 subjects all receiving istradefylline 40 mg/day all instances these were isolated events. Increases in glucose that occurred while on study medication were 3 in the placebo group and 1 in the istradefylline group. Increases in BUN occurred in 7.8% of the istradefylline treated group and 10 % of the placebo group. None of the increases in BUN were accompanied by a concomitant increase in creatinine. There were no instances of renal failure or clinically significant electrolyte derangement reported during the trial. Mean group change values and individual subject change values for BUN and creatinine did not suggest declining renal function.

18.4.1 ECG Changes

Six (4.7%) subjects in the istradefylline group and 3 (4.5%) subjects in the placebo group had values that met the criteria for PCS ECG values at anytime during the study. None of the potentially clinically significant findings in either treatment group was considered significant in light of the pre-existing cardiac findings in these subjects.

Table 7.5 ECG Change Parameters (Adapted fro Kyowa Table)

	Placebo	Istradefylline 40 mg/day
Mean Change in Heart Rate Baseline to wk 12 (bpm)	-2.1	-1.8
Mean change in P-R Interval Baseline to Wk 12 (msec)	0.2	-2.3
Mean QTc Wk 12 (msec)	423.2	423.3
Mean Change QTc baseline –Wk 12 (msec)	-4.2	-0.2

19 COMMON ADVERSE EVENTS

The reviewers analysis of common treatment related adverse events was performed using the agency's MAED adverse event data mining software. A tabulation of the events coded by the preferred terms is provided in the table below. Further analysis of the higher level terms,

higher level group terms and system organ class and standardized MedDRA queries were conducted and none of these additional explorations yielded significant additional information.

Table 8.1-Reviewer's Tabulation of Common Adverse Events (MAED)

	6002 US 005 study	
	Preferred Terms by p-Value (for PTs that occur more than once)	
	Treatment Group	
Preferred Term	**Placebo**	**Istradefylline 40 mg/day**
(MedDRA v5-0)	**(N=66)**	**(N=130)**
BACK PAIN	8 (12.1%)	4 (3.1%)
ORTHOSTATIC HYPOTENSION	3 (4.5%)	0 (0.0%)
DYSKINESIA	10 (15.2%)	40 (30.8%)
FALL	10 (15.2%)	9 (6.9%)
MUSCLE STRAIN	3 (4.5%)	1 (0.8%)
DEPRESSION	4 (6.1%)	2 (1.5%)
CONSTIPATION	1 (1.5%)	9 (6.9%)
PARKINSON'S DISEASE	0 (0.0%)	5 (3.8%)
UPPER RESPIRATORY TRACT INFECTION	0 (0.0%)	5 (3.8%)
BLOOD ALKALINE PHOSPHATASE INCREASED	0 (0.0%)	4 (3.1%)
GASTROOESOPHAGEAL REFLUX DISEASE	0 (0.0%)	4 (3.1%)
HYPERHIDROSIS	0 (0.0%)	4 (3.1%)
MUSCLE RIGIDITY	0 (0.0%)	4 (3.1%)
LIPASE INCREASED	4 (6.1%)	3 (2.3%)
DERMATITIS CONTACT	0 (0.0%)	3 (2.3%)
PARAESTHESIA	0 (0.0%)	3 (2.3%)
PARKINSONISM	0 (0.0%)	3 (2.3%)
ABDOMINAL PAIN UPPER	2 (3.0%)	1 (0.8%)
PERIORBITAL HAEMATOMA	2 (3.0%)	1 (0.8%)
OEDEMA PERIPHERAL	5 (7.6%)	5 (3.8%)
ANOREXIA	1 (1.5%)	6 (4.6%)
ABNORMAL DREAMS	0 (0.0%)	2 (1.5%)
ARTHRITIS	0 (0.0%)	2 (1.5%)
CONFUSIONAL STATE	0 (0.0%)	2 (1.5%)
COUGH	0 (0.0%)	2 (1.5%)
DRY MOUTH	0 (0.0%)	2 (1.5%)
MUSCLE TIGHTNESS	0 (0.0%)	2 (1.5%)
OSTEOPENIA	0 (0.0%)	2 (1.5%)
PSYCHOMOTOR HYPERACTIVITY	0 (0.0%)	2 (1.5%)
PYREXIA	0 (0.0%)	2 (1.5%)
VISION BLURRED	0 (0.0%)	2 (1.5%)
RASH	1 (1.5%)	5 (3.8%)
BALANCE DISORDER	3 (4.5%)	3 (2.3%)
HALLUCINATION	5 (7.6%)	6 (4.6%)
INSOMNIA	6 (9.1%)	17 (13.1%)
NAUSEA	6 (9.1%)	17 (13.1%)
BASAL CELL CARCINOMA	2 (3.0%)	2 (1.5%)
SLEEP DISORDER	1 (1.5%)	4 (3.1%)

VOMITING	1 (1.5%)	4 (3.1%)
DIZZINESS	4 (6.1%)	11 (8.5%)

The common adverse event reported with greatest frequency in the istradefylline treated group compared to placebo (30.8% vs 15.2%) was dyskinesia Insomnia, nausea dizziness, falls, constipation and muscle strain were all more likely in the istradefylline group with a frequency of >5% the treatment group.

19.1 Safety Conclusion

Safety analysis of the 6002-US-005 study did not find evidence for a safety signal suggesting a significant potential for harm. The adverse events were similar in type and frequency as those encountered with other medications used to treat the motor symptoms of Parkinson's disease. Dyskinesia is reported more frequently in the istradefylline treated group compared to placebo therefore the potential for worsening or emerging dyskinesia should be included in the adverse events section of the product label.

19.2 Risk-Benefit Conclusion

Istradefylline demonstrates a statistically significant benefit in terms of the primary outcome measure, the reduction in the percent of the awake part of the day spent in the OFF state. Many of the secondary endpoints are related to the primary endpoint merely expressing OFF time from a different perspective, "Total Off hours vs Percent Off time". Secondary variable describing ON time are related to Off time because the motor states are exclusive, so the less time spent in the awake OFF state would appear as an increase in ON time. Comparison of the mean hours spent asleep did not reveal a significant difference between the istradefylline and placebo groups (≤ 0.25-0.5 hours). The majority of secondary outcome measures still do not demonstrate a statistically meaningful difference between the placebo and istradefylline treated groups. Two secondary endpoints that are frequently selected as primary or co-primary outcome measures in clinical trials in Parkinson's disease are the UPDRS total score and subscale scores and the CGI-I. Both of these secondary outcome measures do not demonstrate a statistically significant benefit of the istradefylline treated group compared to the placebo group. The UPDRS and the CGI-I are designed to convey clinical information about patient function or improvement. The results of the 6002-US-005 study indicate the effect of istradefylline 40 mg/day using on a carefully selected primary endpoint may demonstrate statistically significant between group differences. The results of the UPDRS and CGI-I suggest this effect may not be clinically meaningful. The majority of the remaining secondary endpoints fail to a significant benefit supporting the notion that the results of the CGI-I and UPDRS are not due to chance.

The risk associated with istradefylline 40 mg/day appear acceptable overall. Dyskinesia occurred in almost a third of subjects on istradefylline, which is nearly twice the

frequency, observed in the placebo group and it represents a minor counterbalancing factor. These were no cases of life threatening adverse events, idiosyncratic serious adverse events and the incident deaths were not unusual for subjects with Parkinson's disease. The cause of death in the subjects that died during the trial were also not unusual after considering their age and medical history.

6002-US-006

19.3 Clinical Trial Design

Study Title

A 12-Week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study of the Efficacy of Doses of 20 and 60 mg/day Istradefylline as Treatment for Parkinson's Disease in Patients with Motor Response Complications on Levodopa/Carbidopa Therapy (Protocol Number: 6002-US-006)

Test Drug: Istradefylline (KW-6002) 20 mg/day and 60 mg/day

Indication: Parkinson's Disease

Study Design:

A 12-week, double-blind, randomized, parallel-group, placebo-controlled multicenter study to evaluate safety and efficacy

Protocol Identification: 6002-US-006
Protocol Final Version January 30, 2002

Development Phase: 2b

Study Initiation Date: 23 April 2002 (Date of First Dose)

Study Completion Date: October 6, 2003 (Date of Last Dose)

Report Date: 27 April 2006

19.4 Objectives

19.4.1 Primary:

The primary objective of this study was to evaluate the safety and establish the efficacy of 40 mg/day istradefylline for reducing OFF time in subjects with advanced PD treated with levodopa/carbidopa.

19.4.2 Secondary:

The secondary objective of this study was to establish the efficacy of 40 mg/day istradefylline for reducing motor symptoms and improving activities of daily living (ADL) in subjects with advanced PD treated with levodopa/carbidopa.

19.5 Efficacy Endpoints

19.5.1 Primary

Change from baseline in percentage of awake time in the 'Off state at endpoint based on the validly completed patient's 'On/Off diaries.

19.5.2 Secondary Endpoints

- Change from baseline in the percentage of awake time spent in the 'Off state at Weeks 2, 4, 8, and 12 based on the validly completed patient's 'On/Off' diaries.
- Change from baseline in the total hours of awake time spent in the 'Off' state at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off diaries.
- Change from baseline in percentage of awake time spent in the 'On' state without dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off' diaries.
- Change from baseline in the total hours of awake time spent in the 'On' state without dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off' diaries.
- Change from baseline in the percentage of awake time spent in the 'On' state with dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off diaries.
- Change from baseline in the total hours of awake time spent in the 'On' state with dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off' diaries.
- Change from baseline in the percentage of awake time spent in the 'On' state with non-troublesome dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off' diaries.

- Change from baseline in the percentage of awake time spent in the 'On' state with troublesome dyskinesia at Weeks 2, 4, 8, 12, and endpoint based on the validly completed patient's 'On/Off diaries.

Reviewer Comment

The derived secondary endpoint variables concerning the ON or OFF state, all relate to the primary outcome measure. The UPDRS and CGI-I score are not related to the primary or ON/OFF variables and they are regarded as important measures of performance and motor function in PD. The UPDRS and CGI are often selected as co-primary endpoints in pivotal clinical trials of medications seeking agency approval.

- Change from baseline in UPDRS I-IV total score (including 'On' time rating for UPDRS II and UPDRS III subscales), defined as the sum of subscales I, II, III, and IV at Weeks 2, 4, 8, 12, and endpoint.

- Change from baseline in UPDRS II subscale total score in 'On' at Weeks 2, 4, 8, 12, and endpoint.

- Change from baseline in UPDRS III subscale total score in 'On' at Weeks 2, 4, 8, 12, and endpoint.

- Change from baseline in UPDRS III subscale total score in 'Off at Weeks 4, 12, and endpoint.

- Clinical Global Impression Global Improvement at Weeks 2, 4, 8, 12, and endpoint.

In addition, the analysis of ON state without troublesome dyskinesia, defined as the sum of ON state without dyskinesia and ON state with non-troublesome dyskinesia, were **added after the unblinding of treatment codes:**

20 DEMOGRAPHICS

Table 1-Demographics (Adapted from Kyowa table)

Demographic Characteristic	Placebo (N=77)	Istradefylline 20 mg/day (N=163)	Istradefylline 60 mg/day (N=155)	Total (N=395)
Age (yrs)				
Mean	63.0	65.0	63.5	64.0
SD	12.05	9.59	10.08	10.31
Median	63.0	66.0	65.0	65.0
Range (min-max)	38 to 87	36 to 87	36 to 83	36 to 87
Sex (n [%])				
Male	54 (70.1)	104 (63.8)	106 (68.4)	264 (66.8)
Female	23 (29.9)	59 (36.2)	49 (31.6)	131 (33.2)
Race (n [%])				
Caucasian	73 (94.8)	151 (92.6)	141 (91.0)	365 (92.4)
Black	0	2 (1.2)	4 (2.6)	6 (1.5)
Asian	1 (1.3)	7 (4.3)	2 (1.3)	10 (2.5)
Hispanic	1 (1.3)	1 (0.6)	4 (2.6)	6 (1.5)
American Indian	0	1 (0.6)	0	1 (0.3)
Other	2 (2.6)	1 (0.6)	4 (2.6)	7 (1.8)

There were no significant difference between the treatment groups in age. The racial and gender disparity is typical for the Parkinson's population and are similar in all treatment groups.

20.1 Parkinson's Disease Characteristics at Baseline

Table-2 Parkinson's Disease History at Baseline (Intent-to-treat Population) (Adapted from Kyowa Table)

Characteristic	Placebo (N=77)	Istradefylline 20 mg/day (N=163)	Istradefylline 60 mg/day (N=155)	Total (N=395)
Time since diagnosis (years)				
n[a]	54	98	95	247
Mean	8.69	9.24	7.94	8.62
SD	5.002	5.275	4.017	4.781
Median	7.80	8.75	7.40	8.20
Range (min to max)	2.4 to 32.3	2.1 to 31.9	1.7 to 16.2	1.7 to 32.3
Time since onset of motor complications (years)				
n[a]	40	74	84	198
Mean	3.81	3.71	3.27	3.54
SD	2.694	3.830	3.035	3.288
Median	2.95	2.55	2.30	2.55
Range (min-max	0.4 to 9.3	0.1 to 26.2	0.2 to 15.8	0.1 to 26.2

Note: Duration of PD history was calculated relative to the screening visit date.
[a] Included only subjects who had no missing value for both the month and year of the event time.
SD = standard deviation; min = minimum; max = maximum
Source: End-of-Text Table 14.1.4.1 and Listing 16.2.4

APPEARS THIS WAY ON ORIGINAL

20.1.1 Levodopa Adjustment

After randomization, no changes were made to the levodopa treatment regimen without first consulting the Investigator. Decreases in the total daily dose of levodopa/carbidopa because of adverse events other than worsening of symptoms associated with PD were permitted. The Medical Monitor was consulted prior to decreasing the levodopa/carbidopa dose because of adverse events associated with symptoms of PD. After the adverse event was alleviated, increases in the total daily dose of levodopa/carbidopa to the baseline level were permitted. Changes in the interval between levodopa/carbidopa doses were not allowed at anytime during the study.

Table 3 Parkinson's Disease Characteristics at Baseline Percentage of Awake Time Per Day Spent in the OFF State (Primary endpoint) (Intent-to-treat Population) (Adapted from Kyowa Table)

	Percentage of Awake Time per Day			
Characteristic	Placebo (N=77)	Istradefylline 20 mg/day (N=163)	Istradefylline 60 mg/day (N=155)	Total (N=395)
In an OFF state[a]				
Mean	36.56	34.81	35.07	35.25
SD	14.336	14.701	13.748	14.241
Median	36.90	32.40	35.10	34.20
Range (min to max)	4.2 to 81.4	8.2 to 82.5	6.2 to 72.4	4.2 to 82.5

Table 4 Parkinson's Disease Characteristics at Baseline Total Hours of Awake Time Per Day (Intent-to-treat Population) (Adapted from Kyowa Table)

	Hours of Awake Time Per Day		
Characteristics	Placebo (N=77)	Istradefylline 20 mg/day (N=163)	Istradefylline 60 mg/day (N=155)
In an OFF state[a]			
Mean	6.31	5.72	5.81
SD	2.591	2.502	2.339
Median	6.30	5.30	5.80
Range (min to max)	0.8 to 12.3	1.3 to 14.8	1.0 to 13.0

Reviewer Comment

The demographic characteristics at baseline with regards to age race and gender distribution are typical for clinical trials in PD. The disease history at baseline does not reveal significant difference between any of the treatment groups. The percent of the awake time per day spent in the off state is slightly greater in the placebo group suggesting they are worse at baseline compared to the two istradefylline treated groups. The total hours of awake time spent in the OFF state is also slightly worse at baseline in the placebo group.

21 STATISTICAL ANALYSIS PLAN

All efficacy analyses were carried out based on data from the ITT population. In addition, analyses of the change from baseline by study visit and at endpoint in percentage and total hours of awake time per day spent in an OFF state were carried out based on the modified ITT population using both the observed-case and worst-case imputation approaches. The supportive analysis on the EFF population was not conducted as proposed.

For purposes of the analysis method describe below, a pooling strategy for Investigators was employed based on the enrollment summary of all subjects randomized for each Investigator. Investigators with less than 10 subjects randomized were pooled into 6 groups based on geographic location (Northeast, Midwest 1, Midwest 2, Midwest 3, Southwest, and Southeast). This pooling strategy was implemented prior to unblinding treatment codes.

All efficacy variables (except CGI-I) were analyzed using the 2-way analysis of variance (ANOVA). An analysis of covariance **(ANCOVA) was used as a supportive analysis for testing the treatment effects as specified in the SAP.** The ANOVA model contained terms for investigator and treatment. The ANCOVA model contained terms for investigator, treatment, and baseline as a covariate. Treatment-by-investigator interaction for the primary efficacy variable was tested at the 2-sided alpha of 0.150, and was found to be not statistically significant (p-value = 0.365 for ANOVA and p-value = 0.168 for ANCOVA). The normality assumption for the primary efficacy variable was tested using Shapiro-Wilk test for the residuals from ANOVA and ANCOVA, respectively, at the alpha level of 0.05 and were found to be statistically significant (p-value < 0.0001 for ANOVA and p-value = 0.003 for ANCOVA. Even though normality assumptions for ANOVA and ANCOVA were not met, the analyses of the normalized (using Tukey's, without Tukey's rank transformation for the baseline covariate for ANCOVA model) ranks of the change from baseline in the percentage and total hours of awake time per day in an OFF state based on the same ANOVA and ANCOVA models were performed and showed similar results. In the ANOVA model for the primary efficacy variable, the p-values without and with Tukey's rank transformation were 0.169 and 0.201, respectively. In ANCOVA model for the primary efficacy variable, the p-values without and with Tukey's rank transformation were 0.049 and 0.066, respectively. The analyses for the percentage of awake time per day spent in an OFF state at all study visits and total hours of

For all secondary efficacy variables (except CGI-I), only the main effects ANOVA model with terms for Investigator and treatment was used. An ANCOVA model with Investigator, treatment, and the corresponding Baseline as a covariate was performed as a supplementary analysis for all secondary efficacy variables. The CGI-I was analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by investigator.

21.1.1 Sample Size Determination (Kyowa Description)

The sample sizes of the treatment groups were based on the expected difference between treatment groups in the percentage of time OFF from Baseline to Endpoint for the ITT population. A total of 130 subjects in each of the istradefylline groups were planned to be randomized to obtain at least 112 subjects in each istradefylline group. For the placebo group, 65 subjects were planned to be randomized to obtain at least 56 subjects in the ITT population. The sample size of each group was sufficient to provide 80% power to detect statistical significance at the 2-sided alpha level of 0.050 for treatment group differences greater than or equal to 50% of the applicable standard deviation. The actual numbers of subjects analyzed in the primary analysis were 163 subjects in the 20 mg/day istradefylline group, 155 subjects in the 60 mg/day istradefylline group, and 77 subjects in the placebo group.

22 EFFICACY

22.1 Primary Outcome Variable

Table-5
Kyowa's Analysis of The primary Efficacy Endpoint: Change From Baseline at Endpoint in Percentage of Awake Time Per Day Spent in an OFF State (Intent-to-treat Population)

	Percentage of Awake Time Per Day Spent in an OFF State[a]			
Visit	Placebo (N=77)	Istradefylline 20 mg/day (N=163)	Istradefylline 60 mg/day (N=155)	Overall p-value[b]
Baseline				
n	77	163	155	
Mean	36.56	34.81	35.07	
SD	14.336	14.701	13.748	
Median	36.90	32.40	35.10	
Min to max	4.2 to 81.4	8.2 to 82.5	6.2 to 72.4	
Endpoint				
n	75	162	148	
Mean	32.09	26.87	26.80	
SD	18.328	15.376	15.263	
Median	33.50	25.70	25.80	
Min to max	0.0 to 89.1	0.0 to 76.0	0.0 to 75.7	
Change from Baseline at Endpoint				
n	75	162	148	
Mean	-4.27	-7.94	-8.13	
SD	17.214	15.518	14.164	
Median	-3.90	-7.35	-8.65	
Min to max	-50.1 to 50.6	-67.9 to 32.7	-56.8 to 51.9	
ANOVA				0.169
LS mean	-4.07	-7.72	-7.84	
LS mean difference (versus placebo)		-3.65	-3.77	
p-value (versus placebo)[c]		0.088	0.082	
ANCOVA				0.049
LS mean	-3.47	-7.83	-7.96	
LS mean difference (versus placebo)		-4.36	-4.49	
p-value (versus placebo)[c]		0.026	0.024	

[a] Based on subjects' valid ON/ OFF PD diary data from observed-case analysis.
[b] The overall p-value based on Type III Sums of squares F-test with 2 degrees of freedom for ANOVA or ANCOVA.
[c] P-value for individual comparisons (istradefylline groups versus placebo group) based on least squares means from 2-way ANOVA, including terms for Investigator and treatment or ANCOVA, including terms for Baseline, Investigator, and treatment. At Endpoint, a closed testing procedure was used to test for treatment effects.
LS Mean = least squares mean; SD = standard deviation, min = minimum; max = maximum
Source: End-of-Text Table 14.2.2.1, and Statistical Tests Tables 16.1.9.1.1.1 and 16.1.9.1.1.2

22.2 Key Secondary Outcome Variables

Table-6
Kyowa's Presentation of Total Hours of Awake time Spent in the OFF State

	Total Hours of Awake Time Per Day Spent in an OFF State[a]			
Visit	Placebo (N=77)	Istradefylline 20 mg/day (N=163)	Istradefylline 60 mg/day (N=155)	Overall p-value[b]
Baseline				
n	77	163	155	
Mean	6.31	5.72	5.81	
SD	2.591	2.502	2.339	
Median	6.30	5.30	5.80	
Min to max	0.8 to 12.3	1.3 to 14.8	1.0 to 13.0	
Endpoint				
n	75	162	148	
Mean	5.44	4.50	4.42	
SD	3.181	2.662	2.545	
Median	5.30	4.30	4.00	
Min to max	0.0 to 16.0	0.0 to 13.5	0.0 to 11.5	
Change from Baseline at Endpoint				
n	75	162	148	
Mean	-0.82	-1.22	-1.39	
SD	3.071	2.610	2.390	
Median	-0.70	-1.20	-1.50	
Min to max	-10.0 to 8.3	-13.3 to 6.8	-9.3 to 7.0	
ANOVA				0.335
LS Mean	-0.80	-1.19	-1.35	
LS Mean Difference (versus placebo)		-0.39	-0.55	
p-value (versus placebo)[c]		0.286	0.140	
ANCOVA				0.065
LS Mean	-0.60	-1.24	-1.37	
LS Mean Difference (versus placebo)		-0.64	-0.77	
p-value (versus placebo)[c]		0.055	0.023	

[a] Based on subjects' valid ON/ OFF PD diary data from observed-case analysis.
[b] The overall p-value based on Type III Sums of squares F-test with 2 degrees of freedom for ANOVA or ANCOVA.
[c] P-value for individual comparisons (istradefylline groups versus placebo group) based on least squares means from 2-way ANOVA, including terms for Investigator and treatment or ANCOVA, including terms for Baseline, Investigator, and treatment. At Endpoint, a closed testing procedure was used to test for treatment effects.

LS Mean = least squares mean; SD = standard deviation, min = minimum; max = maximum
Source: End-of-Text Tables 14.2.2.3 and Statistical Tests Tables 16.1.9.2.3.1 and 16.1.9.2.3.2

Table 7-Additional Key Secondary Outcome 6002-US-006

Parameter	Istradefylline 20 mg/d,ay	Istradefylline 60 mg/day
CGI-I (Min, Much or Very Improved)	49.1% , p=0.666 (Placebo 45.5%)	55.6%, p=0.136 (Placebo 45.5%)
UPDRS total (I-IV) at endpoint LMS difference vs placebo	ANOVA = -0.44, p=0.709 ANCOVA = -0.08, p=0.943	ANOVA = -0.66, p=0.578 ANCOVA = -0.82, p=0.475
UPDRS Motor Part III in On and Off states (LMS difference vs placebo, p value)	On ANCOVA = -0.30, p=0.732 Off ANCOVA = -0.99, p=0.352	On ANCOVA = -0.87, p=0.320 Off ANCOVA = -1.28, p=0.239

22.3 Efficacy Conclusions:

The results of study 6002-US-006 do not support the efficacy claim for the sought indication at either dose of istradefylline studied using the sponsor's pre-specified methods of analysis (ANOVA) of the primary outcome variable. The supporting ANCOVA analysis demonstrates a statistically significant between group difference between both the 20 mg and 60 mg/day istradefylline groups and the placebo treated group. Key secondary endpoints (UPDRS and CGI-I), which are not related to the primary outcome variable, do not find a significant difference between the placebo and istradefylline treated groups regardless of the method of analysis (ANOVA or ANCOVA). **Based on the analysis of the available data the trial results do not support the sponsor's efficacy claim for istradefylline at the 20 mg dose.** Of the two doses of istradefylline studied in the trial, the sponsor is only seeking approval of the 20 mg dose. The number of dropouts in the istradefylline 60 mg group is a matter of concern but the number of completed subjects was within the limits of the assumptions made in the sponsor's sample size calculations.

23 SUBJECT DISPOSITION

Table 8 Kyowa's Subjects Disposition Table

Status	Placebo (N=77) n (%)	Istradefylline 20 mg/day (N=163) n (%)	Istradefylline 60 mg/day (N=155) n (%)
All Subjects Randomized:	77 (100.0)	163 (100.0)	155 (100.0)
Safety Population[a]	77 (100.0)	163 (100.0)	155 (100.0)
Intent-to-Treat Population[b]	77 (100.0)	163 (100.0)	155 (100.0)
Completed:			
Week 2	74 (96.1)	162 (99.4)	144 (92.9)
Week 4	72 (93.5)	157 (96.3)	137 (88.4)
Week 8	70 (90.9)	153 (93.9)	132 (85.2)
Completed Double-blind Treatment Period	69 (89.6)	152 (93.3)	126 (81.3)
Discontinued Study Prematurely	8 (10.4)	11 (6.7)	29 (18.7)
Reason for Discontinuation from Study			
Lack of efficacy	0	1 (0.6)	2 (1.3)
Adverse event	5 (6.5)	6 (3.7)	16 (10.3)
Protocol violation or non-compliance with study drug	2 (2.6)	2 (1.2)	5 (3.2)
Subject withdrew consent	1 (1.3)	2 (1.2)	3 (1.9)
Other	0	0	3 (1.9)

[a] All randomized subjects who received at least 1 dose of study drug.
[b] All randomized subjects who received at least 1 dose of study drug and had a Baseline and at least 1 post-baseline efficacy measurement.
Source: End-of-Text Table 14.1.2 and Listing 16.2.2

23.1 Subjects Who Discontinued

Istradefylline 20 mg/day
Seven subjects who discontinued from the study were tracked to the following reason:

Cardiac Arrest (1)
Worsening PD or symptoms (3)
Dyskinesia (1)
Overdose of Sinemet (1)
Hallucinations (1)

Istradefylline 60 mg/day

Twenty-one of the subjects who discontinued from the study were tracked to the following reasons:

Worsening PD or lack of efficacy (4)
Nausea (4)
Dyskinesia (6)
Lost to follow up (1)
Fall (1)
Abnormal Labs (1)
Renal Failure (1) (see discussion below)
Did not feel right (1)
Leg cramps (1)
Scheduled for Deep Brain Stimulation Surgery (1)

Reviewer Comment

18.7% of the group that received istradefylline 60 mg/day discontinued study participation before completion of the trial. The difference in the number of patients that discontinued in the istradefylline 60 mg group is approximately 3 times that of the placebo and istradefylline 20 mg group. Dyskinesia was the reason given for discontinuing participation in the trial more frequently in the 60 mg group. The subject who quit the trial in anticipation for Deep Brain Stimulation surgery also reported dyskinesia as a reason for electing surgical treatment. The disproportionate number of dropouts suggests poor tolerability of the 60 mg/day dose and it would be a counterbalancing factor against a claim for efficacy at the 60 mg dose supported by the 6002-US-006 study data. Patients who smoke may require a dose of 60 mg/day but their exposure and adverse effects would be similar to nonsmoking patients who take 40 mg/day.

24 SAFETY

The data from the 6002-US-006 trial is included in the safety analysis of pools I and V of the ISS. The individual AEs described below are significant and merit discussion because they have temporal relationship to starting study medication, resolve with discontinuing study medication and indicate major organ system abnormality. A confounding factor is the abnormal lab values or pre-existing clinical abnormality, prior to medication exposure, concomitant medications and the absence of re-challenge data.

24.1 Individual Subject Changes

Subject (b) (6) (increased ALT, AST, LDH, CPK, aldolase, and total bilirubin), a 44-year-old Caucasian male subject diagnosed with PD, who received istradefylline 60mg/day. On Day 56, the subject experienced increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood lactate dehydrogenase (LDH), increased blood creatine phosphokinase (CPK), and increased aldolase. On Day 58, he experienced increased blood total bilirubin. The subject was withdrawn from treatment on Day 58.

Subject (b) (6) **Summary of Laboratory Values**

Lab Parameter	Normal Range	Day -1 16 Oct	Week 2 28 Oct	Week 4 7 Nov	Week 8 11 Dec	Week 12[a] 13 Dec	Unsch 16 Dec	Unsch 18 Dec	Unsch 3 Jan
ALT	6-43 U/L	41	38	44 H	69 H	38	45 H	47 H	18
AST	11-36 U/L	33	33	42 H	152 HA	96 H	37 H	27 H	20
LDH	53-234 U/L	136	145	150	322 H	166	127	135	112
CPK	18-198 U/L	194	177	464 H	5892 H	1699 H	232 H	135	83
Aldolase	3-21µmol/L	6.8	5.4	9.7 H	106.6 H	--	12.9 H	8.2 H	3.7
Total Bilirubin	1.2-7.6 U/L	22 H	15	15	17	22 H	21	14	15

[a] Early discontinuation.
A = Potentially clinically significant (see Preface B); H = above the upper limits of the normal range; Unsch = unscheduled visit.
Note: Potentially clinically significant criteria were not established for CPK and aldolase.

The increased LDH was resolved on Day 58; increased bilirubin was resolved on Day 61; increased AST and CPK were resolved on Day 63; and increased aldolase and ALT were resolved on Day 79.

Reviewer Comment

The subjects AST, ALT and CPK were near the ULN at the baseline visit and the total bilirubin was approximately 3 X ULN at baseline. The subject should not have been permitted to enter the trial based on the elevated bilirubin. The abnormal AST and ALT may be a result of worsening hepatobilary obstructive disease or caused by rhabdomyolysis. The reason for the elevation in CPK and aldolase is not mentioned in the sponsor's narrative. The temporal association of istradefylline to the increase in hepatic transaminases and CPK and resolution

after withdrawal suggests istradefylline may be associated to either potential cause of liver function test abnormalities.

Subject (b) (6) (acute renal failure), a 78-year-old Caucasian male subject diagnosed with PD, had a significant medical history of arrhythmia, diverticulitis, Stage II chronic kidney disease, hematuria, left and right knee joint replacement, gout, hypercholesterolemia, and arthritis. The subject received istradefylline 60 mg/day. On Day 14, the subject experienced acute renal failure. The subject was withdrawn from treatment on Day 22.

Subject (b) (6) **Summary of Laboratory Values**

Lab Parameter	Normal Range	Day -1 17 Jun	Week 2 1 Jul	Unscheduled 7 Jul	Unscheduled 9 Jul	Week 12[a] 15 Jul
BUN	1.4-10.4 mmol/L	12.1 HA	14.6 HA	20.3 HA	17.5 HA	11.8 HA
Creatinine	40-137 µmol/L	133	150 H	203 HA	186 HA	124
Sodium	135-145 mmol/L	139	138	139	136	140
Potassium	3.4-5.4 mmol/L	5.9 HA	--	5.9 HA	5.8 HA	5.4
Phosphate	2.9-5.7 U/L	3.7	4.1	--	2.8 L	1.7 L

[a] Early discontinuation
A = Potentially clinically significant (see Preface B); H = above the upper limits of the normal range; L = below the lower limits of the normal range

Concomitant medications at the time of the AE included atenolol 50 mg (arrhythmias), selegiline 5-10 mg (PD), tocopherol 400 IU (general health), allopurinol 300 mg (gout), gemfibrozil 600 mg (hypercholesterolemia), valdecoxib 10 mg (arthritis), and pergolide 0.75 mg (PD). The event was considered resolved on Day 28.

Reviewer Comment

This subject had a history of mild pre-existing renal insufficiency prior to enrollment but there is no recommended istradefylline dose reduction in subjects with renal impairment. The subject had a clear worsening of renal function after starting istradefylline 60 mg/day, which improved with medication withdrawal. The possible cause for adverse event may be associated with a drug-drug interaction involving istradefylline or drug-disease interaction since the cause for the subjects renal insufficiency was not included in the sponsor's narrative.

24.2 Safety Conclusion

There were no deaths reported during this trial and there were no unique safety concerns besides the two cases discussed in the safety section. The case of elevated hepatic transaminases and renal failure provide insufficient evidence to establish a cause and effect relationship.

6002-US-013

24.3 Clinical Trial Design

Title

A 12-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter, Fixed-Dose Study to Evaluate the Efficacy and Safety of a 20 mg/day Oral Dose of KW-6002 (Istradefylline) as Treatment for Parkinson's Disease in Patients with Motor Response Complications on Levodopa/Carbidopa Therapy

Indication: Parkinson's Disease

Study Design: A double-blind, multicenter study to evaluate efficacy and safety

Protocol Identification: 6002-US-013

Development Phase: 3

Study Initiation Date: 14 July 2004 (Date of First Dose)

Study Completion Date: 21 November 2005 (Date of Last Dose)

Report Date: 06 December 2006

24.4 Objectives (stated by the sponsor)

24.4.1 Primary

The primary objective of this study was to evaluate the efficacy of 20 mg/day istradefylline for reducing the percentage of awake time per day spent in the OFF state in subjects with Parkinson's disease treated with levodopa/carbidopa who have motor response complications.

24.4.2 Secondary

- The efficacy of 20 mg/day istradefylline for reducing the total hours of OFF time

- The change in total hours of ON time and percentage of ON time without dyskinesia, with dyskinesia, with non-troublesome dyskinesia, with troublesome dyskinesia, and without troublesome dyskinesia (the change in total hours of ON time and percentage of ON time without troublesome dyskinesia was added to the statistical analysis plan (SAP) prior to the database lock/unblinding)

- The change in Unified Parkinson Disease Rating Scale (UPDRS) Motor Examination Subscale III score and in Activities of Daily Living (ADL) Subscale II score

- The change in Parkinson's Disease Questionnaire (PDQ-39 [sum of questions 1 to 39] and PDQ-8 [sum of questions 7, 12, 17, 25, 27, 31, 35, and 37]), and Medical Outcomes Study 36-Item Short Form (SF-36)

- The Patient Global Impression - Improvement scale (PGI-I)

- The change in the Clinical Global Impression - Severity of Illness scale (CGI-S)

- The safety of 20 mg/day istradefylline by changes in safety parameters

24.4.3 Key Inclusion Criteria(modified from sponsors list)

- Subjects male or female and at least 30 years of age

- Met United Kingdom's Parkinson's Disease Society (UKPDS) brain bank criteria (Step 1 and Step 2) for Parkinson's disease

- Subjects who had Parkinson's disease in Stages 2-4 while in the OFF state on the Modified Hoehn and Yahr Scale

- Subjects who had been on levodopa for at least 1 year, and had been on a stable Parkinson's disease regimen within the normal therapeutic limits including levodopa for at least 4 weeks before Baseline

- Subjects who took at least 3 doses of levodopa per day

- Subjects who had predictable end-of-dose wearing-off

- Subjects who had an average of at least 180 minutes of OFF time per day on the two 24-hour ON/OFF patient diaries prior to the Baseline visit

25 EFFICACY ENDPOINTS

25.1 Primary

Change from baseline in percentage of awake time in the 'Off state at endpoint based on the validly completed patient's 'On/Off diaries.

Reviewer comment

The primary outcome variable is the same for all 5 of the pivotal trials.

25.2 Secondary

Secondary endpoints based on the subject's valid 24-hour ON/OFF Patient Diary:

- Change from baseline to endpoint in total hours of awake time per day spent in the OFF state
- Total hours of awake time per day spent in the OFF state at Weeks 2, 4, 8, and 12 (including actual values at Endpoint)
- Percentage of awake time per day spent in the OFF state at Weeks 2, 4, 8, and 12.

ON State Without Dyskinesia

- Percentage of awake time per day spent in the ON state without dyskinesia at Weeks 2, 4, 8, and 12, and endpoint
- Total hours of awake time per day spent in the ON state without dyskinesia at Weeks 2, 4, 8, and 12, and endpoint

ON State With Dyskinesia

- Percentage of awake time per day spent in the ON state with dyskinesia at Weeks 2, 4, 8, and 12, and endpoint; and
- Total hours of awake time per day spent in the ON state with dyskinesia at Weeks 2, 4, 8, and 12, and endpoint.

ON State With Non-troublesome Dyskinesia

- Percentage of awake time per day spent in the ON state with non-troublesome dyskinesia at Weeks 2, 4, 8, and 12, and endpoint

- Total hours of awake time per day spent in the ON state with non-troublesome dyskinesia at Weeks 2, 4, 8, and 12, and endpoint.

ON State With Troublesome Dyskinesia

- Percentage of awake time per day spent in the ON state with troublesome dyskinesia at Weeks 2, 4, 8, and 12, and endpoint

- Total hours of awake time per day spent in the ON state with troublesome dyskinesia at Weeks 2, 4, 8, and 12, and endpoint.

ON State Without Troublesome Dyskinesia

- Percentage of awake time per day spent in the ON state without troublesome dyskinesia at Weeks 2, 4, 8, 12, and endpoint

- Total hours of awake time per day spent in the ON state without troublesome dyskinesia at Weeks 2, 4, 8, and 12, and endpoint

Based on UPDRS

1. UPDRS Subscale II (in both ON and OFF states) score (ADL) at Weeks 2, 4, 8, and 12, and Endpoint; • UPDRS Subscale III score (Motor Examination) at Weeks 2, 4, 8, and 12, and endpoint

2. UPDRS Subscale II and III total score at Weeks 2, 4, 8, and 12, and endpoint. For all UPDRS subscales, a lower score indicates a better-perceived health status.

Based on Clinical Global Impression

- CGI-S at Weeks 2, 4, 8, and 12, and Endpoint. A subject was assessed on the severity of illness according to a 7-point scale with illness described as: 1) normal/not at all ill; 2) borderline ill; 3) mildly ill; 4) moderately ill; 5) markedly ill; 6) severely ill; or 7) among the most extremely ill.

Based on Parkinson's Disease Questionnaire

- PDQ-39 total score and subscale scores at Weeks 4 and 12, and Endpoint

- PDQ-8 score at Weeks 4 and 12, and Endpoint. For the PDQ-39 scale, a lower score indicates a better-perceived health status. Higher scores are consistently associated with the more severe symptoms of the disease such as tremor and stiffness.

Based on Short Form-36

- SF-36 summary scores and subscales at Weeks 4 and 12, and Endpoint. For the SF-36, a higher score indicates a better-perceived health status.

Based on Patient Global Impression

- PGI-I (actual values only) at Weeks 2, 4, 8, and 12, and Endpoint. The individual categories were scored as: 1) moderate improvement (or greater); 2) mild improvement; 3) no change from Baseline; 4) mild deterioration; or 5) moderate deterioration (or greater).

The secondary efficacy variables of UPDRS Subscale II and III total score and the PDQ-8 score described above were not specified in the protocol but were defined in the final SAP, which was completed prior to the database lock and unblinding of this study.

Reviewer Comment

The secondary outcome variable the same as those selected in the other pivotal trials, including the derived variable relating ON and OFF time. This study added quality of life endpoints (PDQ-39 and the SF-36) and subjects global impression (PGI-I). These secondary outcome variables provide insight to differences in perceived function and how subjects feel on istradefylline compared to placebo group.

26 STATISTICAL ANALYSIS PLAN

The last observation carried forward (LOCF) approach was used to define the endpoint for the efficacy variables. The primary efficacy analysis was based on the ITT analysis set.

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

All continuous supportive and secondary efficacy variables were analyzed using the main effects ANCOVA model.

The CGI-S, change from Baseline for CGI-S (categorical summaries), and PGI-I variables were analyzed using a Cochran-Mantel-Haenszel (CMH) test using modified ridit scores and stratifying by Investigator.

26.1.1 Sample Size Calculation

A sample size of 100 subjects for each group provided 80% power to detect a difference with an effect size of 40% between the 20 mg/day istradefylline group and the placebo group at the two-sided 5% significance level using a t-test. To account for a small percentage of subjects who were not expected to qualify for the ITT analysis set (i.e., less than 5%), 105 subjects were to be randomized to each group for a total of 210 subjects. Actual enrollment was 116 subjects in the 20 mg/day istradefylline group and 115 subjects in the placebo group. Of these subjects, 230 received at least 1 dose of study drug.

26.1.2 Subject Baseline Characteristics

Table 3.1-Demographics (Kyowa)

Demographic Characteristic	Placebo N=115	Istradefylline 20 mg/day N=115	Total N=230
Age (years)			
Mean	63.7	63.3	63.5
SD	10.15	9.47	9.79
Median	63.0	63.0	63.0
Range (min-max)	36 to 87	37 to 84	36 to 87
Sex (n [%])			
Male	77 (67.0)	76 (66.1)	153 (66.5)
Female	38 (33.0)	39 (33.9)	77 (33.5)
Race (n [%])			
Caucasian	105 (91.3)	106 (92.2)	211 (91.7)
Black	4 (3.5)	2 (1.7)	6 (2.6)
Asian	5 (4.3)	1 (0.9)	6 (2.6)
Hispanic	1 (0.9)	1 (0.9)	2 (0.9)
American Indian	0	1 (0.9)	1 (0.4)
Other[a]	0	4 (3.5)	4 (1.7)
Height (cm)			
Mean	172.64	172.63	172.63
SD	10.249	8.670	9.472
Median	173.00	173.00	173.00
Range (min-max)	139.7 to 195.6	152.4 to 190.0	139.7 to 195.6
Weight[b] (kg)			
Mean	81.13	80.65	80.89
SD	18.643	18.360	18.464
Median	79.40	78.90	78.90
Range (min-max)	43.3 to 137.1	44.5 to 135.0	43.3 to 137.1
BMI (kg/m^2)			
Mean	27.08	26.92	27.00
SD	5.226	5.139	5.172
Median	26.80	26.30	26.40
Range (min to max)	17.7 to 44.9	17.2 to 41.0	17.2 to 44.9
Current Smoker			
Yes (n [%])	7 (6.1)	4 (3.5)	11 (4.8)
No (n [%])	108 (93.9)	111 (96.5)	219 (95.2)

[a] "Other" included Iranian, Middle Eastern, Hawaiian (South Pacific Islander), and Italian.
[b] At Screening visit.
SD = standard deviation; min = minimum; max = maximum; cm = centimeter; kg = kilogram m = meter
Source: End-of-Text Table 14.1.3, Appendix 16.2, Listing 16.2.4.1

Reviewer Comment

There were no significant differences at baseline in the demographic characteristics between the istradefylline and placebo groups. The percentage of smokers was small both groups, which is common is studies of patients with PD.

Table 3.2-Parkinson's Disease Baseline Characteristics (Kyowa)

Characteristic	Placebo N=115	Istradefylline 20 mg/day N=115	Total N=230
Time since diagnosis (years)			
Mean	8.83	10.03	9.43
SD	4.445	5.501	5.026
Median	7.80	8.70	8.05
Range (min to max)	0.1[a] to 24.2	1.3 to 36.8	0.1[a] to 36.8
Time since Initiation of levodopa (years)			
Mean	7.54	8.62	8.08
SD	4.512	5.467	5.030
Median	6.90	8.10	7.50
Range (min to max)	1.2 to 24.2	1.1 to 31.8	1.1 to 31.8
Time since onset of motor response complications (years)			
Mean	3.56	3.99	3.78
SD	3.299	3.723	3.516
Median	2.10	3.00	2.80
Range (min to max)	0.1 to 14.7	0.1 to 24.8	0.1 to 24.8

[a] Subject No. (b) (6) had an onset of Parkinson's disease value reported as 0.1 years. The same subject began levodopa therapy 3.8 years before and had an onset of motor complications 1.5 years prior to study entry. The time since diagnosis of Parkinson's disease was queried.
Note: Duration of Parkinson's disease history was calculated relative to the Screening visit date.
SD = standard deviation; min = minimum; max = maximum
Source: End-of-Text Table 14.1.4.1 and Appendix 16.2, Listing 16.2.4.2

Table 3.3-Parkinson's Disease Characteristics at Baseline: Percentage of Awake Time Per Day (Kyowa)

Characteristic	Placebo N=115	Istradefylline 20 mg/day N=115	Total N=230
In the OFF state[a]			
n[b]	115	113	228
Mean	38.63	39.56	39.09
SD	11.577	14.220	12.934
Median	38.20	38.00	38.10
Range (min to max)	17.6 to 64.7	11.4 to 84.2	11.4 to 84.2

Subjects in the placebo group and in the group that received istradefylline 20 mg/day did not differ significantly at baseline with respect to the primary outcome variable, age or baseline disease characteristics.

Changes in Parkinson's Medications

Changes in the interval between levodopa/carbidopa doses was not allowed. A decrease in the total daily dose was permitted, if the established interval between daily was not changed. If clinical conditions permitted, the investigator could readjust the daily dosage of levodopa/carbidopa to the level present at study entry but no higher.

Levodopa Adjustment

Patients could not make any changes in their treatment regimen without consulting the investigator first. Decreases in the total daily dose of levodopa/carbidopa consistent with good clinical care was permitted (e.g., dose reduction to treat levodopa-related adverse events). A change in the interval between levodopa/carbidopa doses was not allowed.

Adjustment of Other Antiparkinsonian Medications

Once the patient was randomized, doses of other antiparkinsonian medications could be decreased to control levodopa-related AEs only (1) after an attempt was made to adjust the patient's Sinemet™ regimen and this was unsuccessful or (2) if the AE is specific to that agent (e.g., urinary retention due to an anticholinergic). Otherwise, doses of other antiparkinsonian medications were required to remain unchanged throughout the study.

27 SUBJECT DISPOSITION

Table 4.1 Subject Disposition (Kyowa)

Status	Placebo N=115 n (%)	Istradefylline 20 mg/day N=116 n (%)
All Subjects Randomized	115 (100.0)	116 (100.0)[a]
Safety Analysis Set[b]	115 (100.0)	115 (99.1)
Intent-to-Treat Analysis Set[c]	113 (98.3)	112 (96.6)
Per-Protocol Analysis Set[d]	99 (86.1)	100 (86.2)
Completed		
Week 2	111 (96.5)	113 (97.4)
Week 4	107 (93.0)	110 (94.8)
Week 8	103 (89.6)	109 (94.0)
Completed 12-Week Double-blind Treatment Period	103 (89.6)	104 (89.7)
Discontinued Study Prematurely	12 (10.4)	12 (10.3)
Reason for Discontinuation from Study		
Lack of efficacy	1 (0.9)	0
Adverse events	7 (6.1)	6 (5.2)
Protocol violation	1 (0.9)	5 (4.3)
Subject withdrew consent	3 (2.6)	0
Other[e]	0	1 (0.9)

[a] Subject No. (b) (6) was randomized to the istradefylline group but did not take any study drug and was discontinued from the study. This subject was not included in any efficacy or safety analyses.
[b] All randomized subjects who took at least 1 dose of study drug.
[c] All randomized subjects who took at least 1 dose of study drug and had a Baseline and at least 1 post-Baseline 24-hour ON/OFF Parkinson's disease patient diary.
[d] Subjects who are in the ITT analysis set and who complete 12 weeks of treatment with no major protocol violations.
[e] Reason for other (subject number (b) (6)) was "missed scheduled visits".
Source: End-of-Text Table 14.1.2 and Listing 16.2.1

27.1 Subjects Who Discontinued Prematurely

Reasons for discontinuing given in the individual subject listings because of AE Istradefylline 20 mg/day

Tremor (1)
Dyskinesia (1)
Increased lipase (1)
Anxious (1)
Urosepsis (1)
Congestive Heart Failure (1)

Reviewer Comment

One subject listed as "other" in the istradefylline 40 mg/day group, should be re-classified as a protocol violation. None of the subjects who discontinued because of an AE experienced a life-threatening AE or had other "designated medical events".

28 EFFICACY ANALYSIS

Table 5.1-Primary Efficacy: Change from Baseline at Endpoint in Percentage of Awake Time Per Day Spent in the OFF State - Observed-Case Analysis (Intent-to-Treat Analysis Set) (Kyowa Table)

	Percentage of Awake Time Per Day Spent in the OFF State[a]		
Visit	Placebo N=113	Istradefylline 20 mg/day N=112	p-value[b]
Baseline			
n	113	112	
Mean	38.72	39.81	
SD	11.612	14.029	
Median	38.20	38.10	
Min to max	17.6 to 64.7	14.6 to 84.2	
Endpoint			
n	113	112	
Mean	33.74	30.48	
SD	17.416	16.315	
Median	32.80	26.70	
Min to max	0.0 to 91.9	0 to 72.4	
Change from Baseline at Endpoint			
n	113	112	
Mean	-4.97	-9.34	
SD	15.468	15.909	
Median	-4.30	-8.85	
Min to max	-58.4 to 43.6	-59.5 to 29.5	
LS mean	-4.92	-9.49	0.025
95% CI (of change)	(-7.76, -2.08)	(-12.43, -6.56)	
LS mean difference (versus placebo)		-4.57	
95% CI (versus placebo)		(-8.55, -0.59)	

[a] Based on valid 24-hour ON/OFF Parkinson's disease patient diary data from observed-case analysis.
[b] The p-value is based on the Type III sums of squares F-test with one degree of freedom from the main effects ANCOVA with terms for Baseline, Investigator, and treatment.
CI = confidence interval; LS Mean = Least Squares mean; SD = standard deviation, min = minimum; max = maximum
Source: End-of-Text Table 14.2.1.1.1, and Statistical Test Table 16.1.9.1.1.1

28.1 Key Secondary outcome Variables

Change in total hours of awake OFF time per day.

The difference between the total awake time spent in the OFF state was significant in favor of the istradefylline 20 mg/day treated group. The least means square difference compared to placebo= -0.73 with p=0.033, which was also statistically significant.

Table 5.2-Summary of Change from Baseline at Endpoint in UPDRS Characteristics (Intent-to-Treat Analysis Set) (Kyowa Table)

	UDPRS Scores at Endpoint	
Characteristic	Placebo N = 113	Istradefylline N = 112
UPDRS Subscale II Score[a] (ON State)		
n	110	111
Baseline (mean)	6.7	6.8
LS Mean Change	-0.9	-0.3
LS Mean Difference (versus placebo)		0.5
p-value (versus placebo)[b]		0.211
UPDRS Subscale II Score[a] (OFF State)		
n	111	109
Baseline (mean)	17.8	18.1
LS Mean Change	-1.7	-1.2
LS Mean Difference (versus placebo)		0.4
p-value (versus placebo)[b]		0.376
UPDRS Subscale III Score[c] (ON State)		
n	112	107
Baseline (mean)	22.8	24.0
LS Mean Change	-2.0	-2.9
LS Mean Difference (versus placebo)		-0.9
p-value (versus placebo)[b]		0.411
UPDRS Subscale II and III Total Score[d]		
n	109	105
Baseline (mean)	47.3	49.2
LS Mean Change	-4.5	-4.5
LS Mean Difference (versus placebo)		-0.1
p-value (versus placebo)[b]		0.972

[a] UPDRS Subscale II Score = the Sum of UPDRS Questions 5 to 17 (Activities of Daily Living) in the ON state and in the OFF states; a lower score indicates a more favorable response.
[b] The p-value is based on the Type III sums of squares F-test with 1 degree of freedom from the main effects of ANCOVA with terms for Baseline, Investigator, and treatment.
[c] UPDRS Subscale III Score = Sum of UPDRS Questions 18 to 31 (Motor Examination); a lower score indicates a more favorable response.
[d] UPDRS Subscale II and III Total Score = Sum of UPDRS Questions 5 to 17 (in both the ON and OFF states) and sum of UPDRS Questions 18 to 31 (Motor Examination); a lower score indicates a more favorable response.
LS = least squares
Source: UPDRS Subscale II Scores: End-of-Text Tables 14.2.8.1 and 14.2.8.2 and Statistical Test Tables 16.1.9.8.1 and 16.1.9.8.2; UPDRS Subcale III Total Scores: End-of-Text Table 14.2.8.3 and Statistical Test Table 16.1.9.8.3; UPDRS Subscale II and III Total Scores: End-of-Text Table 14.2.8.4; and Statistical Test Table 16.1.9.8.4

Reviewer Comment

Parts II (ADL) and III (motor) of the UPDRS represent two important measures of how subjects function. Both the part II and III individual and combined scores have been used in many other registrations studies of approved products, as primary outcome variables. The results of the sponsors analysis indicates despite the statistically significant difference in the primary endpoint (% awake on time spent in OFF state) favoring istradefylline, subjects receiving istradefylline did not function better than subjects who received placebo.

Table 5.3-Summary of Change from Baseline at Endpoint in CGI-S, PDQ-39, PDQ-8, SF-36, and PGI-I Scores (Intent-to-Treat Analysis Set) (Kyowa)

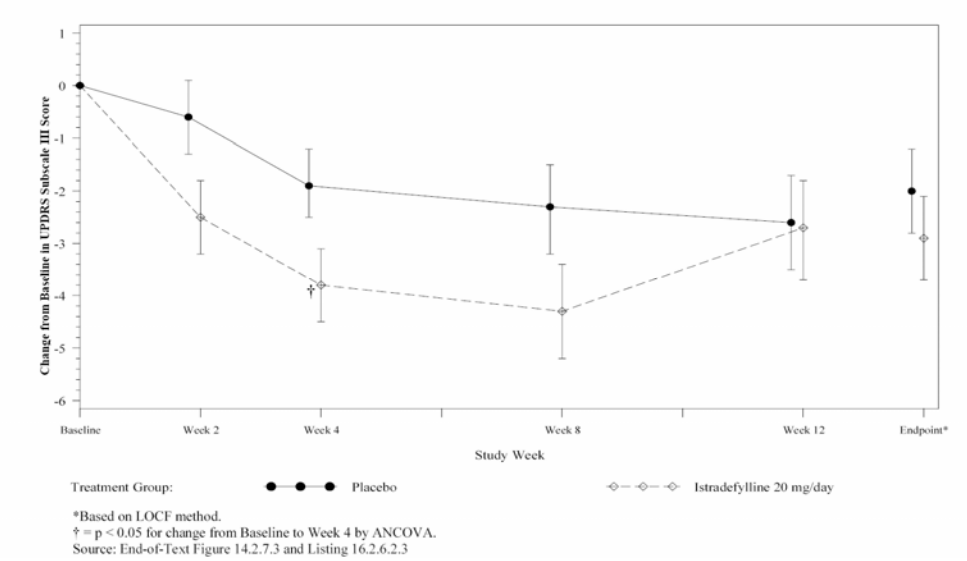
	CGI-S, PDQ-39, PDQ-8, SF-36, and PGI-I Scores at Endpoint	
Assessment	Placebo N = 113	Istradefylline N = 112
CGI-S Total Score [a]		
Baseline (mean)	4.0	4.1
n	113	112
LS Mean Change	-0.1	0.0
LS Mean Difference (versus placebo)		0.0
p-value (versus placebo) [b]		0.516
PDQ-39 Total Score [c]		
Baseline (mean)	29.06	29.72
n	95	99
LS Mean Change	-2.58	-1.45
LS Mean Difference (versus placebo)		1.14
p-value (versus placebo) [b]		0.377
PDQ-8 Total Score [d]		
Baseline (mean)	29.15	31.38
n	107	106
LS Mean Change	-2.35	-1.76
LS Mean Difference (versus placebo)		0.59
p-value (versus placebo) [b]		0.678
SF-36 Total Score [e]		
Baseline (mean)	37.60	37.07
n	109	110
LS Mean Change	1.03	0.33
LS Mean Difference (versus placebo)		-0.71
p-value (versus placebo) [b]		0.370
PGI-I Overall Condition Score (n [%])		
Moderate improvement	14 (12.4%)	19 (17.0%)
Mild improvement	22 (19.5%)	18 (16.1%)
No change from Baseline	45 (39.8%)	40 (35.7%)
Mild deterioration	22 (19.5%)	27 (24.1%)
Moderate deterioration	10 (8.8%)	8 (7.1%)
p-value (versus placebo) [f]		0.640

[a] Higher values indicate a greater severity of illness.
[b] The p-value for treatment effects is based on the Type III sums of squares F-test with 1 degree of freedom from the effects of ANCOVA with terms for Baseline, Investigator, and treatment.
[c] PDQ-39 Total Score = Sum of PDQ-39 Questions 1 to 39, linearly transformed to a scale of 0-100; a lower score indicates a better perceived health status.
[d] PDQ-8 Total Score = Sum of PDQ-39 Questions 7, 12, 17, 25, 27, 31, 35, and 37, linearly transformed to a scale of 0-100; a lower score indicates a better perceived health status.
[e] SF-36 total score = Sum of SF-36 questions 1 to 11; a higher score indicates a better perceived health status.
[f] The p-value is based on the Cochran-Mantel-Haenszel row mean score test using modified ridit scores, stratified by Investigator.
LS Mean = Least Squares mean
Source: CGI-S: End-of-Text Table 14.2.9.3 and Statistical Test Table 16.1.9.9.2; PDQ-39: End-of-Text Table 14.2.10.1 and Statistical Test Table 16.1.9.10.1; PDQ-8 End-of-Text Table 14.2.10.10 and Statistical Test Table 16.1.9.10.10; SF-36: End-of-Text Table 14.2.11.1 and Statistical Test Table 16.1.9.11.1; and PGI-I: End-of-Text Table 14.2.12.1 and Statistical Test Table 16.1.9.12.1

Reviewer Comment

The PDQ-39 is a disease specific questionnaire with 8 components used to investigate health status in trials for PD. A lower score indicates a better functioning and quality of life (0=perfect health, 100=worst health). The PDQ-8 is a shorter version of the PDQ-39 that correlates to the full 39-item scale. The SF 36 is a self-administered scale to measure perceived health status and quality of life. The sponsor's data do not indicate a significant between group differences in perceived quality of life between the placebo and istradefylline on either the SF 36 or PDQ-39. In fact, there is a slight change in the PDQ-39 from baseline to endpoint favoring placebo. The patient rated global impression of improvement also does not indicate subjects feel better on istradefylline. This provided further support to the conclusion istradefylline 20 mg/day does not provide a clinically meaningful benefit compared to placebo.

Table 5.4-UPDRS Part III (motor) Scores by Week



Reviewer Comment

The UPDRS part III scores improve initially in the istradefylline group but after Week 8 scores significantly worsen with confidence intervals that come close to completely overlapping. This may indicate that istradefylline looses it effectiveness with repeated administration. The loss of effect occurs with other non-specific adenosine receptor antagonists (caffeine) but A2A receptor antagonists tested in animal model does not exhibit the loss of effect with chronic administration (Schwarzschild et al)[x].

29 SAFETY (IMPORTANT INDIVIDUAL EVENTS)

Deaths

There was a single death reported during the trial that occurred in a subject. A 52 year-old man treated with placebo was in his home complaining of shortness of breath. He collapsed while speaking to the emergency response operator by phone. Emergency medical services personnel and hospital personnel were unable to resuscitate the patient.

Safety data from this study was reviewed is included in Pool 1 and V of the sponsor's submission to the ISS. The review of this data is included in the safety section of this report. There were no unique safety issues discovered during the review of the safety data from this trial.

30 EFFICACY CONCLUSION

Istradefylline 20 mg/day demonstrates a statistically significant between group difference compared to placebo using the sponsor's primary endpoint and pre-specified analysis. The clinical effect of istradefylline appears to be small and not significant using measures of patient function, perceived of quality of life and health status. Analysis of the UPDRS subscale scores (parts II, III or combined scores) do not indicate there is a statistically significant difference between the istradefylline 20 mg/day group and the placebo group. The patient rated PGI-improvement and the investigator rated CGI-Severity Scale scores do not indicate a statistically significant benefit favoring istradefylline. The lack of significant improvement on scales designed to measure how subjects function and feel so not support approval of istradefylline. The primary outcome measure may be sensitive to small changes in OFF state the change is statistically significant but does not improve quality of life or perceived health status. Despite the effect on the primary outcome variable the sum of the data presented in this clinical trial DO NOT SUPPORT THE APPROVAL of istradefylline 20 mg/day doe the proposed indication.

6002-US-018

30.1 Clinical Trial Design

Title:

A 12-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter, Fixed Dose- Response Study to Evaluate the Efficacy and Safety of 10, 20, and 40 mg/day Oral Doses of KW-6002 (Istradefylline) as Treatment for Parkinson's Disease in Patients with Motor Response Complications on Levodopa/Carbidopa Therapy

Test Drug:	Istradefylline (KW-6002) 10 mg/day, 20 mg, day, 40 mg/day
Indication:	Parkinson's Disease
Study Design:	A 12-week, double-blind, randomized, parallel-group, placebo-controlled, multicenter study to evaluate safety and efficacy
Protocol Identification:	6002-US-018
Development Phase:	Phase 3
Study Initiation Date	23 July 2004 (Date of First Dose)
Study Completion Date	16 November 2005 (Date of Last Dose)
Report Date:	20 December 2006

Trial design

The trial design is the same as the design use in the 6002-US-013 study except there are three dose of istradefylline, which are compared to placebo in a 1:1:1:1 ratio of subjects.

30.1.1 Endpoints

Primary

Change from baseline in percentage of awake time in the 'Off state at endpoint based on the validly completed patient's 'On/Off diaries. The same primary endpoint was used in the 6002-US-005, 006, 013, and 6002-EU-007 studies.

Secondary

The sponsor chose the same secondary endpoints selected for the 6002-US-013 study the reader is referred to the list that appears in the preceding review of the US-013 clinical trial.

30.1.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are the same as the criteria selected for the 6002-US-013 study.

Key Inclusion Criteria

- Subjects who were male or female and at least 30 years of age
- Must meet the United Kingdom's Parkinson's Disease Society (UKPDS) brain bank criteria (Step 1 and Step 2) for Parkinson's disease
- Subjects had Parkinson's disease in Stages 2-4 while in the OFF state on the Modified Hoehn and Yahr Scale
- Subjects who had taken levodopa for at least 1 year, and had been on a stable Parkinson's disease regimen within the normal therapeutic limits including levodopa for at least 4 weeks before Baseline
- Subjects who took at least 3 doses of levodopa per day
- Subjects must have predictable end-of-dose wearing-off
- Subjects must have an average of at least 180 minutes of OFF time per day on the two 24-hour ON/OFF patient diaries prior to the Baseline visit

Changes in Parkinson's Medications

Changes in the interval between levodopa/carbidopa doses was not allowed. A decrease in the total daily dose was permitted, provided that the established interval between daily doses did not changed. If clinical conditions permitted, the investigator could readjust the daily dosage of levodopa/carbidopa to the level present at study entry but no higher.

Table 1.1-Subject Enrollment 6002-US-018 Study

	Placebo	Istradef 10 mg/day	Istradef 20 mg/day	Istradef 40 mg/day	Total
Planned					560
Randomized	154	155	149	152	610
Efficacy Population	146	149	144	145	584
Safety Population	151	153	149	152	605

30.2 Statistical Analysis Plan

30.2.1 Primary Outcome variables

The primary efficacy variable was analyzed using a main effects ANCOVA model with terms for Investigator and treatment as factors and Baseline as a covariate. These terms were fitted as fixed effects and remained in the model regardless of their statistical significance.

30.2.2 Secondary Outcome variables

All continuous secondary efficacy variables were analyzed using the main effects ANCOVA model. Tests for interactions were only summarized on these variables at Endpoint, and no further analyses were conducted, no matter whether any interactions were significant for these variables. Tests for the assumptions of the ANCOVA model were performed on these variables at Endpoint, and no further analyses were conducted, regardless of whether substantial deviations from the assumptions were found for these variables. The CGI-S, change from Baseline for CGI-S (categorical summaries), and PGI-I variables were analyzed using a Cochran-Mantel-Haenszel (CMH) test using modified ridit scores and stratifying by Investigator.

31 DEMOGRAPHICS

Table 2.1 Demographic Characteristics 6002-US-018 Study (Kyowa Table)

Demographic Characteristic	Placebo N=151	Istradefylline 10 mg/day N=153	Istradefylline 20 mg/day N=149	Istradefylline 40 mg/day N=152	Total N=605
Age (years)					
n	151	153	149	152	605
Mean	62.7	63.2	63.9	62.9	63.2
SD	8.26	8.89	9.81	9.26	9.06
Median	63.0	64.0	64.0	62.0	63.0
Range (min to max)	41 to 87	43 to 84	35 to 84	35 to 84	35 to 87
Sex (n [%])					
Male	97 (64.2)	103 (67.3)	103 (69.1)	100 (65.8)	403 (66.6)
Female	54 (35.8)	50 (32.7)	46 (30.9)	52 (34.2)	202 (33.4)
Race/ethnic origin (n [%])					
Caucasian	136 (90.1)	142 (92.8)	143 (96.0)	141 (92.8)	562 (92.9)
Black	0	3 (2.0)	2 (1.3)	2 (1.3)	7 (1.2)
Asian	3 (2.0)	3 (2.0)	1 (0.7)	4 (2.6)	11 (1.8)
Hispanic	8 (5.3)	3 (2.0)	2 (1.3)	4 (2.6)	17 (2.8)
American Indian	1 (0.7)	0	0	0	1 (0.2)
Other[a]	3 (2.0)	2 (1.3)	1 (0.7)	1 (0.7)	7 (1.2)
Current Smoker					
Yes	9 (6.0)	3 (2.0)	9 (6.0)	6 (3.9)	27 (4.5)
No	142 (94.0)	150 (98.0)	140 (94.0)	146 (96.1)	578 (95.5)

Table 2.2-Parkinson's Disease History at Baseline (Safety Analysis Set) (Kyowa)

Characteristic	Placebo N=151	Istradefylline 10 mg/day N=153	Istradefylline 20 mg/day N=149	Istradefylline 40 mg/day N=152	Total N=605
Time since Diagnosis (years)					
n[a]	151	153	149	152	605
Mean	9.14	9.11	8.85	8.47	8.89
SD	5.097	4.745	4.631	4.599	4.768
Median	7.70	8.20	7.90	7.40	7.90
Range (min to max)	1.1 to 27.9	1.0 to 30.4	1.0 to 28.2	1.1 to 22.2	1.0 to 30.4
Time Since Initiation of Levodopa (years)					
n[a]	151	153	149	152	605
Mean	7.77	7.89	7.36	7.18	7.55
SD	5.125	4.729	4.411	4.784	4.767
Median	6.90	6.90	6.50	6.05	6.70
Range (min to max)	1.0 to 25.8	1.0 to 30.4	1.0 to 24.8	0.4 to 20.9	0.4 to 30.4
Time Since Onset of Motor Complications (years)					
n[a]	151	153	148	151	603
Mean	3.73	3.63	3.70	3.40	3.61
SD	3.540	3.656	3.383	3.235	3.452
Median	2.50	2.50	2.90	2.30	2.50
Range (min to max)	0.1 to 17.2	0.1 to 24.4	0.0 to 18.3	0.1 to 18.1	0.0 to 24.4

Note: Duration of Parkinson's disease history was calculated relative to the Screening visit date
[a] Included only subjects who had no missing value for both the month and year of the event time.
SD = standard deviation; min = minimum; max = maximum
Source: End-of-Text Table 14.1.4.1 and Listing 16.2.4.2

Table 2.3-Baseline Percentage of Awake Time Per Day Spent in the OFF State (Kyowa Table)

	Percentage of Awake Time per Day				
Characteristic	Placebo N=151	Istradefylline 10 mg/day N=153	Istradefylline 20 mg/day N=149	Istradefylline 40 mg/day N=152	Total N=605
In the OFF state[a]					
n[b]	148	152	146	150	596
Mean	39.77	39.72	39.65	41.70	40.21
SD	11.419	11.884	12.439	13.400	12.308
Median	38.50	39.10	38.15	40.85	39.35
Range (min to max)	11.4 to 73.2	12.9 to 72.3	17.1 to 74.8	12.9 to 79.7	11.4 to 79.7

Reviewer Comment

There were no significant differences in the baseline demographic factors between the treatment and placebo groups. The between group difference at baseline among the disease related factors, including the Hoehn and Yahr stage was not significant. The total hours of awake time spent in the OFF state was also similar in all treatment groups. The baseline scores in each of the other scales used as secondary outcome variables were also similar across all of the study groups.

32 DISPOSITION

Table 3.1- 6002-US-018 Subject Disposition (Kyowa Table)

Status	Placebo N=154 n (%)	Istradefylline 10 mg/day N=155 n (%)	Istradefylline 20 mg/day N=149 n (%)	Istradefylline 40 mg/day N=152 n (%)	Total N=610 n (%)
All Subjects Randomized	154 (100)	155 (100)	149 (100)	152 (100)	610 (100)
Safety Analysis Set[a]	151 (98.1)	153 (98.7)	149 (100)	152 (100)	605 (99.2)[b]
Intent-to-Treat Analysis Set[c]	146 (94.8)	149 (96.1)	144 (96.6)	145 (95.4)	584 (95.7)
Per-Protocol Analysis Set[d]	130 (84.4)	122 (78.7)	117 (78.5)	117 (77.0)	486 (79.7)
Completed					
Week 2	146 (94.8)	148 (95.5)	148 (99.3)	147 (96.7)	589 (96.6)
Week 4	142 (92.2)	146 (94.2)	141 (94.6)	142 (93.4)	571 (93.6)
Week 8	140 (90.9)	138 (89.0)	134 (89.9)	138 (90.8)	550 (90.2)
Completed 12-Week Double-Blind Treatment Period	140 (90.9)	136 (87.7)	131 (87.9)	135 (88.8)	542 (88.9)
Discontinued prematurely	14 (9.1)	19 (12.3)	18 (12.1)	17 (11.2)	68 (11.1)
Reason for Failure to Complete Double-Blind Treatment Period:					
Lack of efficacy	1 (0.6)	2 (1.3)	1 (0.7)	0	4 (0.7)
Adverse events	7 (4.5)[e]	6 (3.9)[f]	15 (10.1)[g]	15 (9.9)[h]	43 (7.0)
Protocol violation	1 (0.6)	4 (2.6)	1 (0.7)[g]	0	6 (1.0)
Subject withdrew consent	3 (1.9)	5 (3.2)[f]	1 (0.7)	1 (0.7)	10 (1.6)
Other	2 (1.3)	2 (1.3)	0	1 (0.7)	5 (0.8)

32.1 Analysis of Subjects who Discontinued Study Participation in 6002-US-018

The 2 subjects listed a s "other" were lost to follow up without additional information given by the sponsor. The subjects listed as "protocol violations" were all non-compliant with taking study medication or study procedures.

Istradefylline 10 mg/day

Table 3.2-Adverse Events Leading To Discontinuation (N)

Worsening of PD symptoms/OFF/lack of efficacy (3)	Nausea (1)
Insomnia (1)	Confusion (1)
Constipation (1)	

Istradefylline 20 mg/day

Table 3.3-Adverse Events Leading To Discontinuation (N)

Worsening of PD symptoms/OFF/lack of efficacy (2)	Nausea (1)
Non-cardiac chest pressure (1)	Atrial fibrillation (1)
Palpatations (1)	Syncope (1)
Muscle spasm (1)	Back pain (1)
Urinary tract infection/pnuemonia (1)	Rash (1)
Mental fogginess (1)	Left Breast Adenocarcinoma (1)
Elevated liver function tests (1)	Elevated CPK (1)
Psychosis (1)	

Istradefylline 40 mg/ day

Table 3.4-Adverse Events Leading To Discontinuation (N)

Alanine aminotransferase increased (1)	Increased CPK (1)
Angina pectoris/Cardiac ischemia (3)	Constipation (1)
Confusional state/psychosis (2)	Vomiting (1)
Dyskinesia (3)	Worsening PD (2)
Pancreatitis (1)	

Reviewer Comment

One subject who discontinued participation because of worsening PD was inadvertently excluded by the sponsor from the subject listing but is listed in the table below. The case narratives are discussed in the safety portion of this individual study review.

33 EFFICACY OUTCOME

33.1 Primary Efficacy Variable

Table 4.1-Primary Efficacy: Change from Baseline at Endpoint in Percentage of Awake Time Per Day Spent in the OFF State (Intent-to-Treat Analysis Set) (Kyowa)

	Percentage of Awake Time Per Day Spent in the OFF State[a]				
Visit	Placebo N=146	Istradefylline 10 mg/day N=149	Istradefylline 20 mg/day N=144	Istradefylline 40 mg/day N=145	Overall p-value[b]
Baseline					
n	146	149	144	145	
Mean	39.76	39.50	39.66	41.78	
SD	11.484	11.714	12.461	13.127	
Median	38.50	38.90	38.15	40.60	
Min to max	11.4 to 73.2	12.9 to 72.3	17.1 to 74.8	13.2 to 79.7	
Endpoint					
n	146	149	144	145	
Mean	32.18	33.84	33.55	32.70	
SD	15.483	16.999	18.692	18.101	
Median	31.90	33.00	30.85	32.90	
Min to max	0.0 to 62.8	0.0 to 83.1	0.0 to 100.0	0.0 to 100.0	
Change from Baseline at Endpoint					
n	146	149	144	145	
Mean	-7.59	-5.67	-6.11	-9.08	
SD	14.367	14.118	17.619	17.606	
Median	-6.15	-6.20	-6.15	-8.60	
Min to max	-59.9 to 28.6	-40.2 to 37.2	-62.0 to 57.6	-64.6 to 48.2	
LS mean	-8.31	-6.52	-6.81	-8.97	0.475
LS mean difference (versus placebo)		1.79	1.50	-0.66	
p-value (versus placebo)[c]		0.319	0.408	0.714	

[a] Based on subjects' valid 24-hour ON/ OFF Parkinson's disease patient diary data from observed-case analysis.
[b] The overall p-value for treatment effects is among placebo, 20 mg/day, and 40 mg/day groups only, based on the Type III sums of squares F-test with 2 degrees of freedom.
[c] The pairwise p-value (istradefylline groups versus placebo group) based on least squares means from main effects ANCOVA with terms for Baseline, Investigator, and treatment. A closed testing procedure was used to test for treatment effects; however, all p-values are displayed in this table for descriptive purposes.
LS Mean = least squares mean; min = minimum; max = maximum; SD = standard deviation
Source: End-of-Text Tables 14.2.1.1.1 and 14.2.2.1.1 and Statistical Test Table 16.1.9.1.1.1

Reviewer Comment

This study is significant because it is the largest study of istradefylline in terms of the number of subjects enrolled, The treatment arms included each of the doses included in the sponsor's NDA application. Analysis of the primary outcome variable does not demonstrate a statistically significant between group difference from the placebo at the 10 mg, 20 mg and 40

mg/day. The least mean square change from baseline to endpoint visits in the primary outcome variable indicates placebo is superior to istradefylline at the 10 mg/day and 20 mg/day doses. The study fails to demonstrate a statistically significant difference favoring istradefylline for any of the individual doses or for the overall drug effect.

33.2 Secondary Outcome Variables

Table 4.2-Change from Baseline at Endpoint in Total Hours of Awake Time Per Day Spent in the OFF State (Intent-to-Treat Analysis Set) (Kyowa Table)

	Total Hours of Awake Time Per Day Spent in the OFF State[a]				
Visit	Placebo N=146	Istradefylline 10 mg/day N=149	Istradefylline 20 mg/day N=144	Istradefylline 40 mg/day N=145	Overall p-value[b]
Baseline					
n	146	149	144	145	
Mean	6.70	6.55	6.68	6.89	
SD	2.122	2.004	2.175	2.262	
Median	6.50	6.50	6.30	6.80	
Min to max	2.0 to 13.3	2.0 to 11.0	3.0 to 12.3	2.3 to 16.3	
Endpoint					
n	146	149	144	145	
Mean	5.37	5.59	5.63	5.45	
SD	2.673	2.866	3.091	3.074	
Median	5.30	5.80	5.15	5.30	
Min to max	0.0 to 11.0	0.0 to 14.8	0.0 to 16.8	0.0 to 15.0	
Change from Baseline at Endpoint					
n	146	149	144	145	
Mean	-1.32	-0.97	-1.05	-1.45	
SD	2.511	2.389	2.861	2.892	
Median	-1.00	-1.00	-1.00	-1.50	
Min to max	-10.8 to 4.7	-7.3 to 6.3	-10.5 to 9.8	-10.0 to 6.5	
LS Mean	-1.42	-1.11	-1.14	-1.45	0.529
LS Mean Difference (versus placebo)		0.30	0.28	-0.03	
p-value (versus placebo)[c]		0.310	0.360	0.907	

[a] Based on subjects' valid 24-hour ON/ OFF Parkinson's disease patient diary data from observed-case analysis.
[b] The overall p-value for treatment effects is among placebo, 20 mg/day, and 40 mg/day groups only, based on Type III sums of squares F-test with 2 degrees of freedom.
[c] The pairwise p-value (istradefylline groups versus placebo group) based on least squares means from main effects ANCOVA with terms for Baseline, Investigator, and treatment. A closed testing procedure was used to test for treatment effects; however, all p-values are displayed in this table for descriptive purposes.
LS Mean = least squares mean; max = maximum; min = minimum; SD = standard deviation
Source: End-of-Text Table 14.2.2.3.1

Reviewer Comment

The overall treatment effect of istradefylline in not statistically significant compared to placebo. The change from baseline to endpoint in terms of total hours of OFF time indicates placebo is superior to istradefylline at the 10 and 20 mg/day doses. At the 40 mg/day dose, the difference between placebo and istradefylline is minimal.

Table 4.3-Summary of Change from Baseline at Endpoint in UPDRS Characteristics (Intent-to-Treat Analysis Set) (Kyowa Table)

	UPDRS Scores at Endpoint			
Characteristic	Placebo N=146	Istradefylline 10 mg/day N=149	Istradefylline 20 mg/day N=144	Istradefylline 40 mg/day N=145
UPDRS Subscale II Score (ON state)[a]				
Baseline (mean)	6.7	6.6	7.4	6.8
n	145	147	142	145
LS Mean Change	-0.5	-0.3	-0.5	-0.6
LS Mean Diff vs placebo		0.2	0.0	-0.1
p-value (versus placebo)[b]		0.600	0.975	0.820
Overall p-value[c]				0.961
UPDRS Subscale II Score (OFF state)[a]				
Baseline (mean)	17.4	17.9	17.4	17.6
n	143	147	142	144
LS Mean Change	-1.1	-1.8	-1.4	-2.1
LS Mean Diff vs placebo		-0.7	-0.3	-1.0
p-value (versus placebo)[b]		0.143	0.561	0.032
Overall p-value[c]				0.085
UPDRS Subscale III Score (ON state)[d]				
Baseline (mean)	22.6	21.3	22.4	22.0
n	141	141	134	141
LS Mean Change	-0.7	-1.2	-0.7	-2.8
LS Mean Diff vs placebo		-0.5	0.0	-2.1
p-value (versus placebo)[b]		0.572	0.959	0.028
Overall p-value[c]				0.043
UPDRS Subscale II and III Total Score[e]				
Baseline (mean)	46.6	45.9	46.9	46.4
n	138	140	132	140
LS Mean Change	-2.3	-3.4	-2.6	-5.6
LS Mean Diff vs placebo		-1.1	-0.3	-3.3
p-value (versus placebo)[b]		0.424	0.820	0.011
Overall p-value[c]				0.020

[a] UPDRS Subscale II score = the sum of UPDRS questions 5 to 17 (Activities of Daily Living) in the ON state and in the OFF states; a lower score indicates a more favorable response.
[b] The pairwise p-value (istradefylline groups versus placebo group) based on LS means from main effects ANCOVA with terms for Baseline, Investigator, and treatment. A closed testing procedure was used to test for treatment effects; however, all p-values are displayed in this table for descriptive purposes.
[c] The overall p-value for treatment effects is among placebo, 20 mg, and 40 mg treatment groups only, based on the Type III sums of squares F-test with 2 degrees of freedom.
[d] UPDRS Subscale III score = sum of UPDRS questions 18 to 31 (Motor Examination); a lower score indicates a more favorable response.
[e] UPDRS Subscale II and III total score = sum of UPDRS questions 5 to 17 (in both the ON and OFF States) and sum of UPDRS questions 18 to 31 (Motor Examination); a lower score indicates a more favorable response.
Diff = difference; LS Mean = least squares mean
Source: End-of-Text Tables 14.2.8.1, 14.2.8.2, 14.2.8.3, and 14.2.8.4

Reviewer Comment

Istradefylline demonstrates improvement in the UPDRS subscale scores that are inconsistent and do not follow a dose ordered response. The response is only statically significant at the 40 mg/day dose in the Part III subscale (motor) measured in the ON state without and improvement in the part II subscale scores (ADLs) also in the on state. This suggests the effect seen in the part III (motor function) scores at the 40 mg/day dose is not enough to improve activities of daily living.

Table 4.4-Summary of Change from Baseline at Endpoint in CGI-S, PDQ-39, PDQ-8, and SF-36 Scores (Intent-to-Treat Analysis Set) (Kyowa Table)

Assessment	Placebo N=146	Istradefylline 10 mg/day N=149	Istradefylline 20 mg/day N=144	Istradefylline 40 mg/day N=145
CGI-S total score[a]				
Baseline (mean)	3.8	3.7	3.8	3.8
n	146	147	144	145
LS Mean Change	-0.1	-0.1	0.0	-0.2
LS Mean Diff vs placebo		0.0	0.0	-0.1
p-value (versus placebo)[b]		0.678	0.567	0.179
Overall p-value[c]				0.146
PDQ-39 total score[d]				
Baseline (mean)	30.75	31.43	30.26	31.82
n	126	137	134	128
LS Mean Change	-3.94	-3.41	-2.27	-3.51
LS Mean Diff vs placebo		0.53	1.67	0.43
p-value (versus placebo)[b]		0.596	0.098	0.674
Overall p-value[c]				0.226
PDQ-8 total score[e]				
Baseline (mean)	30.30	31.07	30.93	32.09
n	133	145	140	141
LS Mean Change	-4.13	-3.63	-2.58	-3.45
LS Mean Diff vs placebo		0.50	1.56	0.68
p-value (versus placebo)[b]		0.684	0.208	0.581
Overall p-value[c]				0.449
SF-36 (physical components summary score)[f]				
Baseline (mean)	35.87	34.14	35.28	36.17
n	143	146	143	142
LS Mean Change	-0.11	1.19	0.55	1.24
LS Mean Diff vs placebo		1.31	0.66	1.36
p-value (versus placebo)[b]		0.060	0.340	0.051
Overall p-value[c]				0.149
SF-36 (mental health components summary score)[f]				
Baseline (mean)	47.73	49.25	47.13	48.45
n	143	146	143	142
LS Mean Change	1.62	-0.07	-1.28	-0.92
LS Mean Diff vs placebo		-1.69	-2.91	-2.54
p-value (versus placebo)[b]		0.082	0.003	0.009
Overall p-value[c]				0.005
PGI-I overall condition score [n (%)]				
n	146	149	144	145
Moderate improvement	22 (15.1)	30 (20.1)	28 (19.4)	24 (16.6)
Mild improvement	42 (28.8)	35 (23.5)	38 (26.4)	53 (36.6)
No change from Baseline	61 (41.8)	44 (29.5)	49 (34.0)	36 (24.8)
Mild deterioration	18 (12.3)	29 (19.5)	21 (14.6)	27 (18.6)
Moderate deterioration	3 (2.1)	11 (7.4)	8 (5.6)	5 (3.4)
p-value (versus placebo)[b]		0.640	0.953	0.564
Overall p-value[c]				0.795

Footnotes to Table 11.4.1-9:

[a] Higher values indicate a greater severity of illness.

[b] The pairwise p-value (istradefylline groups versus placebo group) based on LS means from main effects ANCOVA with terms for Baseline, Investigator, and treatment. A closed testing procedure was used to test for treatment effects; however, all p-values are displayed in this table for descriptive purposes.

[c] The overall p-value for treatment effects is among placebo, 20 mg, and 40 mg treatment groups only, based on the Type III sums of squares F-test with 2 degrees of freedom.

[d] PDQ-39 total score = sum of PDQ-39 questions 1 to 39, linearly transformed to a scale of 0 - 100; a lower score indicates a better-perceived health status.

[e] PDQ-8 total score = sum of PDQ-39 questions 7, 12, 17, 25, 27, 31, 35, and 37, linearly transformed to a scale of 0 - 100; a lower score indicates a better-perceived health status.

[f] SF-36 summary scores = a higher score indicates a better-perceived health status.

Diff = difference; LS Mean = least squares mean

Source: End-of-Text Tables 14.2.9.3, 14.2.10.1, 14.2.10.10, 14.2.11.1, 14.2.11.2, 14.2.12.1 and Listings 16.2.6.3, 16.2.6.4.2, 16.2.6.5.2, and 16.2.6.6

Reviewer Comment

The PDQ-39 is a PD specific scale indicating subject's perception of their health status and quality of life. The SF-36 is a non-disease specific measure of perceptions of health status and quality of life. The results for the PDQ-39 indicates that the placebo group had a lower (better) score at baseline and that their scores improved to a greater degree than any of the groups treated with istradefylline. The CGI-S and PGI-I (patient rated) scores do not indicate istradefylline improved the site investigator's or patient's perception of their degree of improvement. The SF-36 demonstrated improvement in the mental component only, for the 20 mg and 40 mg/day doses.

34 SAFETY EVALUATION

The safety data for the 6002-US-018 study was reviewed in the analysis of the ISS. Data from this study is included in pools I and V of the ISS.

34.1 Deaths

Placebo Group

Subject (b) (6)

A 67 year-old Caucasian female with a history significant for an aortic valve replacement and atrial fibrillation died on day 23, one day after it was discovered she has mesenteric artery occlusion. The cause of death was listed as a cardiorespiratory arrest.

Istradefylline

Subject (b) (6)

A 61 year-old male who was randomized to istradefylline 40 mg/day became psychotic on study day 7. He was withdrawn from istradefylline and he was hospitalized for psychosis on study day 11. The subject was discharged home and he remained off of study drug. On day 23 the subject was readmitted to the hospital after a suicide attempt by ingestion of multiple medications, excluding study medication. The subject was described as "impaired" and he was referred to hospice with a diagnosis of lithium toxicity, which he ingested during his suicide attempt. The subject died in hospice 52 days following withdrawal from study medication.

Subject (b) (6)

A 72-year-old man with a history of previous myocardial infarction, coronary artery bypass surgery and coronary artery disease was randomized to the istradefylline 10

mg/day group. He was recently discovered to have new lesions on X-ray in the femur and lumbar vertebra. He was admitted to the hospital for difficulty using his leg on study day 21. Study drug was discontinued on day 18 because of non –compliance with study visits. On day 38 the subject collapsed in front of his daughter and he was taken to the hospital. The subject died the next day (day 39) in carcinogenic shock.

34.2 Common Adverse Events

Table 5.1-Incidence of Treatment-Emergent Adverse Events Reported by ≥ 5% of Subjects in Any Group Regardless of Relationship to Study Drug by System Organ Class and Preferred Term (Safety Analysis Set) (Kyowa Table)

MedDRA System Organ Class[a] Preferred Term	Placebo N=151 n (%)	Istradefylline 10 mg/day N=153 n (%)	Istradefylline 20 mg/day N=149 n (%)	Istradefylline 40 mg/day N=152 n (%)
Subjects with Any TEAE	**115 (76.2)**	**126 (82.4)**	**125 (83.9)**	**128 (84.2)**
Nervous System Disorders	57 (37.7)	74 (48.4)	52 (34.9)	66 (43.4)
Dyskinesia	29 (19.2)	33 (21.6)	25 (16.8)	40 (26.3)
Parkinson's disease, worsened	8 (5.3)	17 (11.1)	9 (6.0)	7 (4.6)
Headache	7 (4.6)	7 (4.6)	6 (4.0)	11 (7.2)
Lightheadedness	5 (3.3)	8 (5.2)	6 (4.0)	11 (7.2)
Tremor	8 (5.3)	6 (3.9)	3 (2.0)	1 (0.7)
Gastrointestinal Disorders	26 (17.2)	36 (23.5)	33 (22.1)	37 (24.3)
Nausea	9 (6.0)	11 (7.2)	7 (4.7)	12 (7.9)
Constipation	6 (4.0)	10 (6.5)	11 (7.4)	11 (7.2)
Musculoskeletal and Connective Tissue Disorders	30 (19.9)	36 (23.5)	22 (14.8)	34 (22.4)
Arthralgia	9 (6.0)	12 (7.8)	4 (2.7)	9 (5.9)
Psychiatric Disorders	24 (15.9)	25 (16.3)	30 (20.1)	42 (27.6)
Insomnia	11 (7.3)	10 (6.5)	11 (7.4)	16 (10.5)
Hallucination	2 (1.3)	2 (1.3)	3 (2.0)	9 (5.9)
Infections and Infestations	32 (21.2)	22 (14.4)	19 (12.8)	27 (17.8)
Upper respiratory tract infection	5 (3.3)	4 (2.6)	3 (2.0)	8 (5.3)
General Disorders and Administration Site Conditions	25 (16.6)	17 (11.1)	25 (16.8)	21 (13.8)
Fatigue	7 (4.6)	6 (3.9)	10 (6.7)	6 (3.9)
Investigations	21 (13.9)	11 (7.2)	20 (13.4)	29 (19.1)
Weight Decreased	2 (1.3)	5 (3.3)	4 (2.7)	9 (5.9)
Injury, Poisoning and Procedural Complications	12 (7.9)	17 (11.1)	18 (12.1)	16 (10.5)
Accident	9 (6.0)	9 (5.9)	9 (6.0)	10 (6.6)

Note: If a subject experienced more than 1 adverse event within a SOC, the subject was counted once under that SOC. If a subject had more than 1 adverse event for a particular Preferred Term, the subject was counted once for that Preferred Term
[a] MedDRA dictionary Version 7.0 was used for coding. See Listing 16.2.7.4 for the mapping of the verbatim to the coded term.
MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class; TEAE = treatment-emergent adverse event
Source: End-of-Text Table 14.3.2.3

34.3 Serious Adverse Events

Orthostatic Hypotension

Two subjects experience syncope also termed orthostatic hypotension during the trial both event met criteria for reporting as an SAE. The first subject had a history of orthostatic hypotension that predated enrollment in the trial. The second subject had a single, self-limited episode of syncope on study day 57 while taking istradefylline 20 mg/day. He remained on study medication and on day 75 the subject fell and sustained a fracture of the acetabulum and

ribs. He was hospitalized and during the hospitalization a pulmonary embolism complicated his recovery. There narrative did not mention if the subject's fall was caused by syncope.

Non-invasive ductal carcinoma of the breast

A 62-rear-old female who was randomized to istradefylline 20 mg/day was discovered to have adenocarcinoma of the breast on study day 23. She underwent lumpectomy on study day 41 where a pathological diagnosis was confirmed and clinically staged at T1c. The sponsor's narrative did not state precisely when the subject was withdrawn from study medication but indicated treatment ended.

Myocardial infarction

An 82 year-old Caucasian female with a significant medical history that included coronary artery disease, hypertension, pitting edema of feet, was randomized to istradefylline 40 mg/day. Study medication was discontinued study drug on day 4, but on day 5 of the study, the subject was awakened with chest pain and went to the ER where she was diagnosed with atrial fibrillation and cardiac failure and was admitted to the hospital. She was discharged on Day 9 with a diagnosis of non-Q wave myocardial infarction (probably apical) and atrial fibrillation.

Elevated Lipase

Table 5.2 6002-US-018 Subjects With Elevated Lipase (Kyowa Table)

Center/ Subject	Laboratory Variable	Normal Range[a]	Study Visit: Week -2	Day -1	Week 2	Week 4	Week 8	Week 12/ET
			Placebo					
(b) (6)	Lipase (U/L)	0 to 100	40	45	353H[b] 32 (Day 25)[c]	40	35	37
	Amylase (U/L)	28 to 120	38	40	88	45	41	36
	Trypsin-like Immunoreactivity (ng/mL)	20.5 to 132	34.7	37.2	110.8	29.5	30.9	39.3
			Istradefylline 20 mg/day					
	Lipase (U/L)	0 to 120	29	29	72	26	26	346H[b] 35 (Day 99)[e]
	Amylase (U/L)	28 to 150	51	53	84	44	44	196H 54 (Day 99)[e]
	Trypsin-like Immunoreactivity (ng/mL)	20.5 to 132	54.6	54.7	73.1	41.9	44.5	120.3
	Lipase (U/L)	0 to 100	33	29	46	145H[b]	33	78
	Amylase (U/L)	28 to 120	61	66	68	117	68	73
	Trypsin-like Immunoreactivity (ng/mL)	20.5 to 132	29.0	22.7	38.3	55.4	29.9	119.0
	Lipase (U/L)	0 to 120	38	46	38	41	284H[b]	37
	Amylase (U/L)	28 to 150	62	63	64	67	99	65
	Trypsin-like Immunoreactivity (ng/mL)	20.5 to 132	42.1	48.5	37.9	43.5	599.5H[d]	43.2
			Istradefylline 40 mg/day					
	Lipase (U/L)	0 to 120	44	92	579H[b]	--	--	50[e]
	Amylase (U/L)	28 to 150	117	143	219H	--	--	96[e]
	Trypsin-like Immunoreactivity (ng/mL)	20.5 to 132	26.6	40.9	361.0H	--	--	28.7[e]

[a] Laboratory normal range specific for age of subject.
[b] Value reported as TEAE.
[c] Unscheduled visit (Day of unscheduled visit).
[d] Value met the PCS criteria (amylase and lipase simultaneously ≥ 1.5 x ULN; trypsin-like immuno-reactivity: ≥ 3.0 x ULN).
[e] Early discontinuation on Day 42 for pancreatitis.
-- Not evaluated
ET = early termination; H = above the upper limit of the normal range; ULN = upper limit of normal; PCS = potentially clinically significant
Source: Preface A to Listings 16.2.8.1 to 16.2.8.4, Listings 16.2.7.1 and 16.2.8.2

One subject in the placebo group, 3 subject to the istradefylline 20 mg and 1 in the istradefylline 40 mg group developed a treatment emergent elevation in serum lipase. Subject (b) (6) and (b) (6) had concomitant elevation of trypsin-like immunoreactivity suggesting pancreatitis. Subject (b) (6) was withdrawn from study medication on day 18, when pancreatitis when the lab data became known to the investigator. The sponsor's narrative for this adverse event did not describe the subject as having clinical signs of pancreatitis. Subject (b) (6) experienced an isolated elevation of lipase identified at week 12 but there was no additional information concerning this subject.

Elevated Liver Function Tests

Two subjects were withdrawn from the study because of a TEAL relating to elevated liver enzymes. The first ((b) (6)) was withdrawn from istradefylline 20 mg/day on day 57 of the study because of an ALT of 109 U/L (32 U/L=ULN), AST of 85 U/L (34 U/L=ULN) and Alkaline Phosphatase of 519 U/L (123 U/L=ULN). On day 68 the subject was hospitalized for 2 days. Study medication was withdraw, the subject was also taking 9 concomitant medications, including atorvastatin, known to inhibit CYP3A4 and increase the exposure to istradefylline but regarded as safe for co-administration with istradefylline at a dose of 20 mg/day. Subject

(b) (6) was discontinued from the study because of "hepatic enzymes increased". The abnormal hepatic enzymes were abnormally elevated at baseline ALT= 42 U/L (34 U/L=ULN) on study day 15 and the subject was withdrawn for the study because of elevations in the ALT and AST to > 3X ULN (ALT=130 U/L). Both TEALs were said to be resolved in the sponsor's narrative.

35 EFFICACY CONCLUSION

The 6002-US-018 study results do not demonstrate a significant between group difference in favor of istradefylline in improving the percentage of awake OFF time in subjects with advanced PD at the 10 mg/day, 20 mg/day or 40 mg/day doses. The overwhelming majority of secondary endpoints, including many that reflect how subjects felt and functioned on istradefylline fail to demonstrate a statistically of clinically significant improvement in any of the istradefylline treated groups.

36 SAFETY CONCLUSIONS

The deaths that occurred during the 6002-US-018 trial were from causes that are common for people in the targeted age group and did not suggest istradefylline played a role in causing the deaths. There were no adverse events described in vital sign or clinical exam parameters, which were unusual for the age of the target population. The abnormal laboratory parameters, such as lipase and transaminase elevations did not clearly demonstrate cause and effect but when looking at the pooled safety data there is evidence for a dose effect associated with an increase in AST and ALT that become maximal at the 60 mg/day dose. The reader is referred to the ISS for a more comprehensive discussion of this finding.

6002-EU-007

36.1 Clinical Trial Design

Title

A 16-week, Double-Blind, Placebo-Controlled, Randomised, Parallel-Group, Multicentre, International Study to Evaluate the Efficacy and Safety of 40 mg/day KW-6002 (istradefylline) and that of Entacapone versus Placebo as Treatment for Parkinson's Disease in Patients with Motor Response Complications on Levodopa Therapy.

Test Drug: Istradefylline (KW-6002) or entacapone 200 mg with carbidopa/levopopa

Indication: Parkinson's disease

Study Design: A double-blind, placebo-controlled, multicenter, parallel-group study to evaluate effcacy and safety

Protocol Identification: 6002-EU-007

Development Phase: 3

Study Initiation Date: November 24, 2004 (Date of First Dose)

Study Completion Date: October 03, 2005 (Date of Last Dose)

Report Date: January12, 2007

37 EFFICACY VARIABLES:

37.1 Primary

The primary efficacy variable is the change from baseline in percentage of awake time per day spent in the OFF state at Endpoint. This is the same primary outcome variable used in all of the other pivotal trials.

37.2 Secondary

The sponsor chose the same secondary endpoints selected for the 6002-US-013 and US-018 study the reader is referred to the list that appears in the preceding review of the US-013 and 018 clinical trials.

37.3 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are the same as the criteria selected for the 6002-US-013 study.

Key Inclusion Criteria

- Subjects who were male or female and at least 30 years of age
- Must meet United Kingdom's Parkinson's Disease Society (UKPDS) brain bank criteria (Step 1 and Step 2) for Parkinson's disease
- Subjects who had Parkinson's disease in Stages 2-4 while in the OFF state on the Modified Hoehn and Yahr Scale
- Subjects who had been on levodopa for at least 1 year, and had been on a stable Parkinson's disease regimen within the normal therapeutic limits including levodopa for at least 4 weeks before Baseline
- Subjects who currently took at least 3 doses of levodopa per day
- Subjects who had predictable end-of-dose wearing-off
- Subjects who had an average of at least 180 minutes of OFF time per day on the two 24-hour ON/OFF patient diaries prior to the Baseline visit

38 STATISTICAL ANALYSIS PLAN

38.1 Primary Efficacy Variable

The last observation carried forward (LOCF) approach was used to define the endpoint for the efficacy variables. The primary efficacy analysis was based on the ITT analysis set. The primary efficacy variable was analyzed using a main effects ANCOVA model with terms for investigator and treatment as factors and baseline as a covariate. These terms were fitted as fixed

effects and remained in the model regardless of their statistical significance. The test for treatment effects was carried out from this model.

38.2 Analysis of Supportive and Secondary Efficacy Variables

All continuous supportive and secondary efficacy variables were analyzed using the main effects ANCOVA model. Tests for interactions were only summarized on these variables at Endpoint, and no further analyses were conducted, no matter whether any interactions were significant for these variables. Tests for the assumptions of the ANCOVA model were performed on these variables at Endpoint, and no further analyses were conducted, regardless of whether substantial deviations from the assumptions were found for these variables. The CGI-S, change from Baseline for CGI-S (categorical summaries), and PGI-I variables were analyzed using a Cochran-Mantel-Haenszel (CMH) test using modified ridit scores and stratifying by Investigator.

38.3 Determination of Sample Size

A total, 464 subjects were enrolled at 56 centers in Argentina, Austria, Chile, Estonia, France, India, Italy, Latvia, Lithuania, Russia, the Republic of South Africa, Spain, the UK, and the Ukraine. Of the 464 subjects entered into the double-blind period, 152 were randomized to receive placebo, 159 to receive istradefylline 40 mg/day, and 153 to receive entacapone. A total of 410 subjects completed the study: 147 subjects in the istradefylline group, 130 subjects in the entacapone group, and 133 subjects in the placebo group. A sample size of 130 subjects for each treatment group was estimated to provide 80% power to detect a difference with an effect size of 35% between the 40 mg/day treatment group and the placebo treatment group at the two-sided 5% significance level using a t-test derived from the main effects ANCOVA model. To account for a small percentage of subjects who were not expected to qualify for the ITT analysis set (e.g., fewer than 4%), approximately 135 subjects were to be randomized to each treatment group giving a total of 405 subjects. The entacapone treatment group was not included in the comparison of 40 mg/day istradefylline with placebo, but contributed to the error variance in the ANCOVA model.

38.4 Deviations

In Russia, the randomization treatment blocks were split across centers in error. This was not believed to have had any effect on the results of the study.

39 SUBJECT DISPOSITION

Table 4.1-Subject Disposition (Kyowa Table)

Status	Placebo n (%)	Istradefylline n (%)	Entacapone n (%)	Total n (%)
All Subjects Randomized[a]	152 (100.0)	159 (100.0)	153 (100.0)	464 (100.0)
Safety Analysis Set[b]	152 (100.0)	159 (100.0)	153 (100.0)	464 (100.0)
ITT Analysis Set[c]	151 (99.3)	158 (99.4)	146 (95.4)	455 (98.1)
PP Analysis Set[d]	125 (82.2)	141 (88.7)	124 (81.0)	390 (84.1)
Completed:				
Week 2	150 (98.7)	157 (98.7)	146 (95.4)	453 (97.6)
Week 4	140 (92.1)	157 (98.7)	140 (91.5)	437 (94.2)
Week 6	139 (91.4)	155 (97.5)	136 (88.9)	430 (92.7)
Week 8	137 (90.1)	151 (95.0)	132 (86.3)	420 (90.5)
Week 12	133 (87.5)	149 (93.7)	130 (85.0)	412 (88.8)
Completed 16-Week Double-Blind Treatment Period	133 (87.5)	147 (92.5)	130 (85.0)	410 (88.4)
Discontinued prematurely	19 (12.5)	12 (7.5)	23 (15.0)	54 (11.6)
Reason for Failure to Complete Double-Blind Treatment Period:				
Lack of efficacy	3 (2.0)	2 (1.3)	1 (0.7)	6 (1.3)
Adverse event	10 (6.6)	7 (4.4)	10 (6.5)	27 (5.8)
Protocol violation	1 (0.7)	0	0	1 (0.2)
Subject withdrew consent	3 (2.0)	2 (1.3)	6 (3.9)	11 (2.4)
Other[e]	2 (1.3)	1 (0.6)	6 (3.9)	9 (1.9)

[a] Subject No. (b) (6) was randomized to entacapone but did not meet Exclusion Criterion #13 (ALT > 1.5 times the upper limit of normal). This subject was subsequently randomized to istradefylline under Subject No (b) (6) (See Appendix 16.2.8, Listing 16.2.9.9 for comments relating to this event).

[b] All randomized subjects who took at least 1 dose of double-blind study drug.

[c] All randomized subjects who took at least 1 dose of double-blind study drug and had a Baseline and at least 1 post-Baseline 24-hour ON/OFF Parkinson's disease patient diary.

[d] Subjects who are in the ITT analysis set and who completed 16 weeks of treatment with no major protocol violations.

[e] Two subjects (Subject Nos. (b) (6) discontinued because of lack of improvement; 2 subjects (Subject Nos. (b) (6) discontinued because they felt their condition was worsening; Subject No. (b) (6) did not meet Inclusion criterion 6 and was discontinued on study Day -1; Subject No. (b) (6) relocated; Subject No. (b) (6) was lost to follow-up; Subject No. (b) (6) died; and Subject No. (b) (6) decided to leave upon someone else's advice.

ITT = intent-to-treat, PP = per protocol

Source: End-of-Text Table 14.1.2 and Appendix 16.2.1, Listing 16.2.1

Fifty-four (11.6%) subjects discontinued prematurely; 12 (7.5%) in the istradefylline group, 23 (15.0%) in the entacapone group, and 19 (12.5%) in the placebo group. Among the subjects who withdrew from the study because of an adverse event the fewest number withdrew from the istradefylline treated group 7 (4.4%).

39.1 Changes in Parkinson's Medications

Changes in the interval between levodopa/carbidopa doses was not allowed. A decrease in the total daily dose was permitted, provided the established interval between daily doses did not changed. If clinical conditions permitted, the investigator could readjust the daily dosage of levodopa/carbidopa to the level present at study entry but no higher.

Levodopa Adjustments

Patients obtained levodopa from their usual suppliers and could not make any changes in their treatment regimen without consulting the Investigator first. During the initial 4-week period of the study, adjustment of levodopa dosage, if required, was permitted at the Investigator's discretion. Changes in the interval between levodopa doses was allowed during the initial 4-week period. After Week 4 any adjustment to the levodopa dosing regimen was

considered a deviation from the protocol and could only be authorized by prior written consent following discussion between the Investigator and the Sponsor. Any changes made to any medication (either dosage or regimen) must be recorded in the source documents and on the CRF.

Adjustment of Other Antiparkinsonian Medications:

During the first four weeks of the study changes to the dosing regimen, or discontinuation of other antiparkinsonian medications to control dopamine-related adverse events are only permitted if an attempt has been made to adjust the patient's levodopa regimen and this was unsuccessful, or if the AE is specific to that agent (e.g., urinary retention due to an anticholinergic).

After Week 4 of the study changes to the dose or dosing regimen or discontinuation or addition of other antiparkinsonian medications was considered a deviation from the protocol and could only be authorized after discussion between the Investigator and the Sponsor. Changes made to any medication (either dosage or regimen) must be recorded in the source documents and on the appropriate CRF.

40 DEMOGRAPHIC

Table 5.1-Demographics and Baseline Characteristics (Safety Analysis Set) (Kyowa Table)

Characteristic	Placebo N=152	Istradefylline N=159	Entacapone N=153	Total N = 464
Age (years)[a]				
Mean	62.4	60.8	61.3	61.5
SD	8.60	9.29	10.24	9.41
Median	63.0	61.0	62.0	62.0
Range (min to max)	39 to 80	35 to 81	34 to 87	34 to 87
Gender (n [%])				
Male	92 (60.5)	99 (62.3)	93 (60.8)	284 (61.2)
Female	60 (39.5)	60 (37.7)	60 (39.2)	180 (38.8)
Race (n [%])				
Caucasian	104 (68.4)	108 (67.9)	102 (66.7)	314 (67.7)
Asian	32 (21.1)	34 (21.4)	33 (21.6)	99 (21.3)
Hispanic	14 (9.2)	15 (9.4)	15 (9.8)	44 (9.5)
Other[b]	2 (1.3)	2 (1.3)	3 (2.0)	7 (1.5)

*The distribution of subjects who were current smokers among was similar among the three treatment group.

41 EFFICACY

41.1 Primary Outcome Variable

Table 6.1-Primary Efficacy: Change from Baseline at Endpoint in the Percentage of Awake Time per Day Spent in the OFF State (Intent-to-Treat Analysis Set) (Kyowa Table)

	Percentage of Awake Time Per Day Spent in the OFF State[a]		
Visit	Placebo N=151	Istradefylline N=158	Entacapone N=146
Baseline[b]			
n	151	158	146
Mean	41.49	38.61	40.05
SD	12.257	11.625	13.423
Median	41.70	38.35	39.00
Range (min to max)	14.8 to 82.4	13.8 to 68.6	13.1 to 73.9
Endpoint			
n	151	158	146
Mean	36.73	34.30	32.63
SD	17.311	16.095	17.741
Median	37.80	35.05	31.65
Range (min to max)	0.0 to 81.1	0.0 to 73.9	0.0 to 75.4
Change from Baseline at Endpoint			
n	151	158	146
Mean	-4.76	-4.31	-7.42
SD	15.858	15.544	16.358
Median	-1.20	-3.75	-4.95
Range (min to max)	-82.4 to 34.4	-62.5 to 33.9	-50.7 to 33.4
LS Mean	-4.53	-5.14	-7.82
95% CI (of change)	(-7.02, -2.04)	(-7.58, -2.69)	(-10.34, -5.30)
LS Mean difference (versus placebo)		-0.61	-3.29
95% CI (versus placebo)		(-4.05, 2.83)	(-6.77, 0.19)
p-value (versus placebo)[c]		0.729	0.064

[a] Based on valid 24-hour ON/OFF patient diary from observed-case analysis.
[b] Baseline values were collected from diaries dispensed at Day -1. Subjects with more than 4 invalid entries in any 1 of their 2 daily diaries had to repeat the Baseline (Day -1) visit 7 days later. Subjects failing the validity criterion for a second time were precluded from participating in the study.
[c] The pairwise p-value is based on LS means from main effects ANCOVA with terms for Baseline, Investigator, and treatment.

CI = confidence interval; LS = least squares; max = maximum; min = minimum; SD = standard deviation

Reviewer Comment

The comparison of istradefylline to placebo concerning the primary outcome variable does not find a statistically significant between group difference (p=0.729). The comparison of entacapone to placebo also does not find a statistically significant between group difference however, the difference only narrowly exceeds the pre-specified alpha with a p value=0.06.

41.2 Secondary Outcome Variables

Table 6.2-Change From Baseline at Endpoint in Total Hours of Awake Time Per Day Spent in the OFF State (Intent-to-Treat Analysis Set) (Kyowa figure)

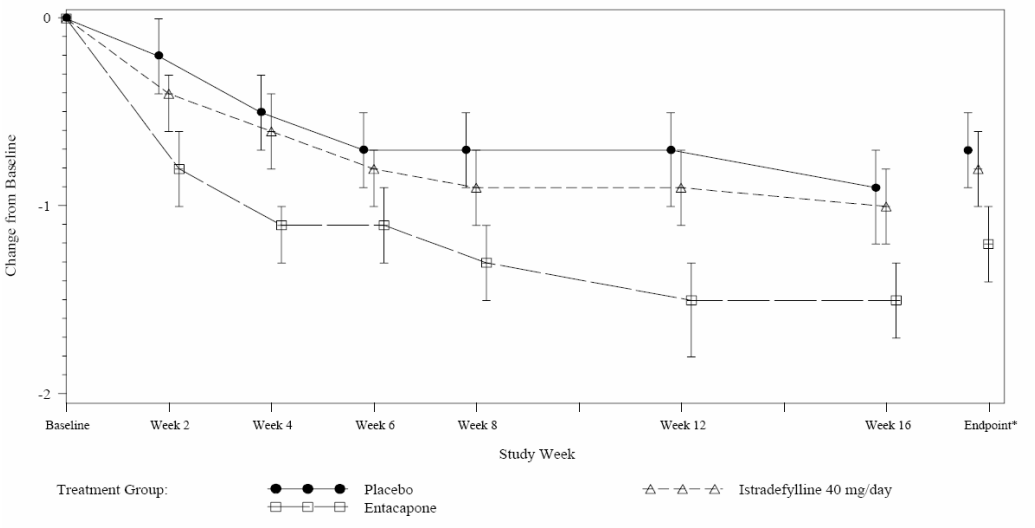


Table 6.3-Change from Baseline at Endpoint in UPDRS Characteristics (Intent-to-Treat Analysis Set) (Modified from Kyowa Table)

UPDRS Scores at Endpoint Characteristic	Placebo	Istradefylline 40 mg/day	Entacapone
UPDRS Subscale III Score (ON state)			
n	148	153	143
Baseline (mean)	27.5	27.4	27.7
LS Mean Change	-3	-4.6	-4.8
LS Mean Difference vs. placebo		-1.6	-1.8
p-value (vs. placebo)b		0.064	0.043
UPDRS Subscale II Score (ON state)			
n	151	156	144
Baseline (mean)	7.3	7.4	7.5
LS Mean Change	-0.8	-1.4	-1.5
LS Mean Difference vs. placebo		-0.6	-0.6
p-value (vs. placebo)b		0.116	0.086

Reviewer Comment

Changes in the UPDRS parts II and III ON scores find that neither drug produced a statistically significant change in UPDRS subscale scores compared to placebo but the p value for entacapone was much closer to being significant.

Table 6.4-Summary of Change from Baseline at Endpoint in CGI-S, PDQ-39, PDQ-8, PGI-I, and SF-36 Scores (Intent-to-Treat Analysis Set) (Kyowa Table)

Assessment	Placebo N=151	Istradefylline N=158	Entacapone N=146
CGI-S total score[a]			
n	151	158	146
Baseline (mean)	4.1	4.0	4.1
LS Mean Change	-0.1	-0.2	-0.3
LS Mean Difference vs. placebo		-0.1	-0.1
p-value (versus placebo)[b]		0.423	0.071
PDQ-39 total score[c]			
n	143	148	141
Baseline (mean)	37.75	36.74	36.39
LS Mean Change	-2.51	-2.74	-3.66
LS Mean Difference vs. placebo		-0.23	-1.15
p-value (versus placebo)[b]		0.847	0.340
PDQ-8 total score[d]			
n	144	158	144
Baseline (mean)	37.71	37.39	35.73
LS Mean Change	-2.45	-2.91	-3.54
LS Mean Difference vs. placebo		-0.47	-1.09
p-value (versus placebo)[b]		0.734	0.434
PGI-I (overall condition score) (n [%])	151 (100)	158 (100)	146 (100)
Moderate improvement	22 (14.6)	30 (19.0)	36 (24.7)
Mild improvement	47 (31.1)	58 (36.7)	51 (34.9)
No change from Baseline	51 (33.8)	48 (30.4)	33 (22.6)
Mild deterioration	22 (14.6)	12 (7.6)	16 (11.0)
Moderate deterioration	9 (6.0)	10 (6.3)	10 (6.8)
p-value (versus placebo)[e]		0.160	0.044
SF-36 (physical components summary score)[f]			
n	144	155	143
Baseline (mean)	38.12	37.98	37.40
LS Mean Change	0.39	1.11	2.36
LS Mean Difference vs. placebo		0.72	1.97
p-value (versus placebo)[b]		0.323	0.008
SF-36 (mental health components summary score)[f]			
n	144	155	143
Baseline (mean)	40.20	41.52	42.31
LS Mean Change	-0.94	0.32	-0.21
LS Mean Difference vs. placebo		1.26	0.74
p-value (versus placebo)[b]		0.192	0.453

[a] Higher values indicate a greater severity of illness.
[b] The pairwise p-value was based on LS means from main effects ANCOVA with terms for Baseline, Investigator, and treatment.
[c] PDQ-39 total score = sum of PDQ-39 questions 1 to 39, linearly transformed to a scale of 0 - 100; a lower score indicates a better-perceived health status.
[d] PDQ-8 total score = sum of PDQ-39 questions 7, 12, 17, 25, 27, 31, 35, and 37, linearly transformed to a scale of 0 - 100; a lower score indicates a better-perceived health status.
[e] The pairwise p-value is based on the Cochran-Mantel-Haenszel row mean score test using modified ridit scores, stratified by Investigator, and involving placebo and each of the respective istradefylline or entacapone treatment groups.
[f] SF-36 total score = sum of SF-36 questions 1 to 11; a higher score indicates a better-perceived health status.

LS = least squares; vs. = versus
Source: End-of-Text Tables 14.2.9.3, 14.2.10.1, 14.2.10.10, 14.2.11.1, 14.2.11.2, 14.2.12.1 and Listings 16.2.6.3, 16.2.6.4.2, 16.2.6.5.2, and 16.2.6.6

Reviewer Comment

Between group differences comparing istradefylline to placebo on all of the secondary outcome variable listed in the table above fail to demonstrate istradefylline is superior to placebo.

42 SAFETY

The 6002-EU-007 study safety data analysis was included in this reviewer's analysis of the ISS. The data from this study was included in the analysis of pools I and V. Individual outliers and safety events are discussed in this individual study review and the ISS. Serious and common adverse events are discussed in the pooled data results contained in the ISS.

42.1 Deaths

There were 3 deaths reported in the trial none occurred in the istradefylline treated group. A single death in the placebo group was due to pneumonia. Two subjects treated with entacapone died during the course of the trial. The first subject withdrew her consent and was taken off study medication on day 59. On day 73 the subject was hospitalized for severe anemia due to a bleeding duodenal ulcer. Her recovery was complicated by a fall and ulnar fracture and sudden respiratory distress; she died on mechanical ventilation due on day 102. Another subject developed a persistently high fever and vomiting on day 32. The environmental temperature was described as high and the subject did not have sign of infection. He was treated with antipyretics and domperidone and the caregivers were advised to bring the subject to the hospital. He died later that evening died the cause of death listed in the narrative was heat stroke but the evidence presented could not exclude infection from an undiscovered source instead of heat stroke.

Table 7.1-Subjects Who Discontinued Treatment Because of Adverse Events (Safety Analysis Set) (Modified Kyowa Table)

Center/ Subject	Gender/Age /Race	Onset Day	End Day	Adverse Event- Preferred Term (Verbatim Term)
		Placebo		
(b) (6)	M/57/C	68	89	Muscle rigidity
	F/65/C	21	Ongoing	Parkinson's disease (worsening of Parkinson's disease)
	F/65/A	56	Ongoing	Bundle branch block left
	M/71/C	58	Unknown	Lethargy
	M/74/C	11	24	Parkinson's disease (exacerbation of Parkinson symptoms)
	F/63/C	17	46	Lightheadedness
		19	46	Hypotension
	F/63/C	31	49	Dyskinesia (increasing of dyskinesias)
	F/66/C	26	29	Cerebrovascular accident
	M/62/C	7	Ongoing	Parkinson's disease (worsening of Parkinson's disease symptoms)
	M/76/C	41	55	Neutropenia
		41	55	Leukopenia
		Istradefylline		
	M/59/C	42	72	Hepatic enzyme increased
	M/49/C	44	94	Agitation (hyperexcitation due to L-dopa overdose)
	F/54/C	1	Unknown	Gastric irritation (gastric intolerance to study medication)
	M/66/C	37	42	Hallucination
	M/55/C	80	100	Hallucination, visual
	F/64/C	42	56	Drug ineffective (absence of levodopa dose effect)

(b) (6)	F/51/C	17	Ongoing	Dyskinesia (worsening of dyskinesia)
				Entacapone
	F/70/C	40	77	Muscle rigidity
	F/59/C	18	44	Dyskinesia (worsening of dyskinesia)
	M/34/A	62	69	Psychotic disorder
		Entacapone		
	F/64/A	17	Ongoing Burning sensation	Moderate
	M/65/C	11	25	Diarrhea
	M/63/C	1	20	Angina unstable
	F/66/O	3	35	Memory impairment
	M/59/O	1	15	Dysphagia (capsule too big to swallow)
	M/70/C	8	9	Atrial fibrillation
	M/56/C	13	Unknown	Dyskinesia (more prolonged dyskinesia)

Individual Laboratory Adverse Events

Table 7.2-Subjects With Potentially Clinically Significant Laboratory Values Reported as TEAEs (Safety Analysis Set) (Kyowa Table)

Center/ Subject	Laboratory Variable and units	Study Visit: Week -2	Day -1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16/ET
Placebo									
Blood bilirubin increased (normal range[a]: 3 to 21 µmol/L)									
(b) (6)	µmol/L	24H	24H	38H[b]	31H	29H	39H[b]	39H[b]	36H[b]
	(mg/dL)	(1.4)	(1.4)	(2.2[b])	(1.8)	(1.7)	(2.3[b])	(2.3[b])	(2.1[b])
Blood amylase increased (normal range[a]: amylase = 28 to 120 U/L; lipase = 0 to 100 U/L; Trypsin-like immunoreactivity = 20.5 to 132.5 ng/mL)									
(b) (6)	Amylase U/L	106	73	124H	152H	209H[b]	127H	245H[b]	63
	Lipase U/L	41	31	69	165H	223H[b]	63	217H[b]	32
	Trypsin-like immunoreactivity ng/mL	70.1	52.8	77.2	552.0H[b]	107.6	64.4	-	39.0
Istradefylline									
Hepatic enzyme increased (normal range[a]: ALT = 6 to 43 U/L; AST = 11 to 36 U/L)									
(b) (6)	ALT U/L	27	57H	29	38	351H[b] 417H[b,d]	-	-	136H[b] 30[d]
	AST U/L	24	34	28	29	188H[b] 177[b,d]	-	-	51H 28[d]
Transaminase increased (normal range[a]: ALT = 6 to 43 U/L; AST = 11 to 36 U/L)									
(b) (6)	ALT U/L	29	36	30	30	-	-	-	72H 29[d]
	AST U/L	24	33	27	35	-	-	-	112H[b] 21[d]
Transaminase increased (normal range[a]: ALT = 6 to 32 U/L; AST = 9 to 34 U/L)									
(b) (6)	ALT U/L	<4L	10	10	7	9	211H[b] 99H[b,d]	16	6
	AST U/L	14	20	16	14	14	113H[b] 62H[d]	15	17
BUN increased and creatinine increased (normal range[a]: BUN = 1.4 to 8.6 mmol/L; creatinine = 31 to 101 µmol/L)									
(b) (6)	BUN mmol/L	5.7	19.6H[b]	5.0	6.8	5.0	4.6	6.8	6.4
	(mg/dL)	(16)	(55[b])	(14)	(19)	(14)	(13)	(19)	(18)
	Creatinine µmol/L	62	380H[b]	62	62	62	53	62	62
	(mg/dL)	(0.7)	(4.3[b])	(0.7)	(0.7)	(0.7)	(0.6)	(0.7)	(0.7)
BUN increased (normal range[a]: BUN = 1.4 to 8.6 mmol/L; creatinine = 40 to 119 µmol/L)									
(b) (6)	BUN mmol/L	9.5H	9.4H	9.6H	8.9H	11.9H[b]	10.1H	10.7H	9.5H
	(mg/dL)	(27)	(26)	(27)	(25)	(33[b])	(28)	(30)	(27)
	Creatinine µmol/L	108	108	113	100	123H	124H	112	124H
	(mg/dL)	(1.2)	(1.2)	(1.3)	(1.1)	(1.4)	(1.4)	(1.3)	(1.4)
Blood sodium decreased (normal range[a]: 135 to 145 mmol/L)									
(b) (6)	mmol/L	142	143	-	142	141	144	122L[b]	144

Center/ Subject	Laboratory Variable and units	Study Visit: Week -2	Day -1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16/ET
Entacapone									
Blood glucose increased (normal range[a]: 3.9 to 6.4 mmol/L)									
(b) (6)	mmol/L	13.8H	9.0 H	13.0H	10.3H	15.2H[b]	14.5H[b]	7.0H	10.7H
	(mg/dL)	(248)	(162)	(234)	(186)	(274[b])	(262[b])	(126)	(193)

[a] Laboratory normal reference range reported for age and gender of subject.

[b] Value PCS: AST ≥ 3.0 x ULN; ALT ≥ 3.0 x ULN; Amylase and Lipase are simultaneously ≥ 1.5 x ULN and Trypsin-like immunoreactivity is ≥ 3.0 x ULN; BUN > 10.7 mmol/L [> 30 mg/dL]); Bilirubin > 34 µmol/L [> 2.0 mg/dL]); Creatinine ≥ 177 µmol/L [≥ 2.0 mg/dL]); Glucose > 13.9 mmol/L [> 250.5 mg/dL]); Sodium > 150 mmol/L).

[c] Subject discontinued from the study because of the TEAE.

[d] Unscheduled visit.

- = Not evaluated.

ALT = Alanine transaminase; AST = Aspartase transaminase; ET = early termination; H = above normal range; L = below normal range; TEAE = treatment-emergent adverse event; ULN = upper limit of normal

Source: Preface A to Tables 14.3.3.4 to 14.3.3.6; Preface B to Tables 14.3.3.7, 14.3.3.8, 14.3.4.6, 14.3.5.8, and 14.3.5.9; Appendix 16.2.7, Listing 16.2.7.1, and Appendix 16.2.8, Listings 16.2.8.2, 16.2.8.5, 16.2.8.5D, 16.2.8.5E, 16.2.8.5H, 16.2.8.5L, 16.2.8.5M, and 16.2.8.5O

Reviewer Analysis

Hepatic Enzymes

Subject (b) (6) withdrew from the study for an adverse event listed as "hepatic enzymes increased". He was randomized to the istradefylline 40 mg/day group and on day 42 he was discovered to have elevated hepatic enzymes. The subject's ALT was mildly elevated (52 U/L) at the baseline visit but returned to normal levels until the week 6 visit. His ALT was > 8 X ULN with a AST > 5 X ULN at the week 6 study visit. The subject was discontinued from the study on day 72 and his hepatic enzymes were returning to but not back to baseline at the conclusion of the study (week 16). The subject's alkaline phosphatase and total bilirubin remained with in the normal range.

Subject (b) (6) had an elevated ALT and AST had an isolated elevation of AST and ALT discovered at the week 8 scheduled visit. The results of the AST and ALT measured at an unscheduled visit at study day 60 found there were returning towards the normal range. The subject's transaminases returned to the normal range by week 12 and remained with in the normal range through out the conclusion of the trial (week 16). The subject's alkaline phosphatase and total bilirubin remained with in the normal range.

Subject (b) (6). The subject was discontinued from study medication on study day 37 because of an unrelated TEAE, hallucination. His AST was greater the 3 X ULN with a elevated ALT that was approximately 2 X ULN. Both the AST and ALT returned to the normal range by day 58 and the alkaline phosphatase and total bilirubin remained with in the normal range.

The remaining laboratory related TEAEs were reported in ≤ 2 subjects in the istradefylline group

43 EFFICACY CONCLUSION

Istradefylline 40 mg/day did not demonstrate statistically significant superiority over placebo for the primary outcome variable or important secondary outcome variables. The effect of istradefylline over placebo compared to the effects of entacapone over placebo, entacapone is consistently numerically superior to istradefylline 40 mg/day with respect to the primary and secondary endpoints.

44 SAFETY CONCLUSIONS

The review of the safety information for the 6002-EU-007 trial is included in the ISS. The data from the trial is contained in safety data pools I and V. The were no unique safety issues identified in the review of this individual trial.

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