Supplementary Material

Efficacy of Istradefylline, an Adenosine A$_{2A}$ Receptor Antagonist, as Adjunctive Therapy to Levodopa in Parkinson's Disease: A Pooled Analysis of 8 Phase 2b/3 Trials

Supplementary File 1

Supplementary Table 1. Summary of primary endpoints and analysis sets for pooled trials

Trial	*Phase*	*Country*	*Primary endpoint units*	*Diary completion*[a]	*Included in 4-study pool*	Placebo	Istradefylline 10 mg/day	20 mg/day	40 mg/day	60 mg/day	Entacapone 200 mg/LD dose	*Reference*
6002-US-005	2b	US/Canada	% OFF	1-2	Yes	66	-	–	129	-	-	LeWitt, et al. (2008) [16]
6002-US-006	2b	US/Canada	% OFF	1-2	No	77	-	163	–	155	-	Stacy, et al. (2008) [13]
6002-US-013	3	US	% OFF	1-2	Yes	113	-	112	–	-	-	Hauser, et al. (2008) [15]
6002-0608	2b	Japan	Hours OFF	4-7	Yes	118	-	115	124	-	-	Mizuno, et al. (2010) [17]
6002-009	3	Japan	Hours OFF	4-7	Yes	123	-	120	123	-	-	Mizuno, et al. (2013) [18]
6002-US-018	3	US/Canada	% OFF	1-2	No	146	149	144	145	-	-	Pourcher, et al. (2012) [14]
6002-EU-007	3	Europe/S. America/ S. Africa/India/UK	% OFF	1-2	No	151	-	–	158	-	146	NA (See

												Supplementary 2)
6002-014	3	US/Canada/Europe/Israel	Hours OFF	3	No	198	-	194	200	-	-	NA (See Supplementary 3)
Total						992	149	848	879	155	146	

[a]Number of daily ON/OFF diaries to be completed during the week preceding baseline and scheduled study visits; Hours OFF, hours/day in the OFF state; ITT, intent-to-treat; LD, levodopa; % OFF, % of awake time in the OFF state.

Supplementary Table 2. Study design comparison

6002-US-005	6002-US-006	6002-US-013	6002-0608	6002-009	6002-US-018	6002-EU-007	6002-014
Design: Double-blind, randomized, placebo-controlled, parallel-group clinical study							
12-week	12-week	12-week	12-week	12-week	12-week	16-week	12-week
Istradefylline 40 mg/day or placebo (2:1 ratio)	Istradefylline 20 or 60 mg/day or placebo (2:2:1 ratio)	Istradefylline 20 mg/day or placebo (1:1 ratio)	Istradefylline 20 or 40 mg/day or placebo (1:1:1 ratio)	Istradefylline 20 or 40 mg/day or placebo (1:1:1 ratio)	Istradefylline 10, 20, or 40 mg/day or placebo (1:1:1:1 ratio)	Istradefylline 40 mg/day or placebo or entacapone (1:1:1 ratio)	Istradefylline 20 or 40 mg/day or placebo (1:1:1 ratio)

Patients were:
- ≥30 years of age, (≥20 years of age in Studies 6002-0608 and 6002-009)
- Diagnosed with PD as determined by the UKPDS criteria
- Modified Hoehn and Yahr scale Stages 2 to 4 in the OFF state (Studies 6002-US-005, 6002-US-006, 6002-US-013, 6002-0608, 6002-009, 6002-US-018, and 6002-EU-007), and in the ON state (Study 6002-014)
- Had end-of-dose wearing-off with an average of ≥2 hours OFF time per day (Studies 6002-US-005, 6002-US-006, 6002-0608, 6002-009, and 6002-014) or 3 hours OFF time per day (Studies 6002-US-013, 6002-US-018, and 6002-EU-007) at study entry; patients in 6002-014 also had levodopa-induced dyskinesia

Levodopa requirements:
- Receiving levodopa and peripheral DOPA-decarboxylase inhibitor (carbidopa or benserazide) for ≥1 year
- Treated with levodopa for at least 1 year and have been on a stable regimen of levodopa for at least 4 weeks before randomization/baseline (as per protocol specification)
  – Studies 6002-US-005 and 6002-US-006: ≥4 doses/day, or ≥3 doses/day if 2 doses were slow-release formulations (no specific levodopa dose requirement)
  – Studies 6002-US-013, 6002-US-018, and 6002-EU-007: ≥3 doses/day (no specific levodopa dose requirement)
  – Studies 6002-0608 and 6002-009: ≥300 mg/day levodopa
  – Study 6002-014 required patients to be taking ≥400 mg/day levodopa plus at least one adjunctive dopaminergic medication approved to treat PD and to have documented levodopa-induced dyskinesia
- Decrease in the total daily dose of levodopa was permitted, if necessary (Investigator's discretion) due to levodopa-related AEs
- Change in either the frequency of levodopa dosing or the interval between levodopa doses was not allowed (exception: Study 6002-EU-007 allowed levodopa dose adjustment during the initial 4 weeks)

Other Parkinson's medications were allowed (and were required in Study 6002-014)

6002-US-005	6002-US-006	6002-US-013	6002-0608	6002-009	6002-US-018	6002-EU-007	6002-014
<td colspan="8">   - Reduction in the dose of anti-Parkinson medication was permitted in order to control dopaminergic-related AEs if a prior reduction in the levodopa dose was unsuccessful or to alleviate AEs thought to be directly related to the agent being adjusted   - Prior anti-Parkinson medication could not be increased, and no new anti-parkinson medication could be added   </td>
<td colspan="8">**Primary endpoint (per protocol):** Change from baseline in OFF time/day expressed as:</td>
% of awake time	% of awake time	% of awake time	Hours	Hours	% of awake time	% of awake time	Hours
<td colspan="8">**Primary statistical methodology:** Analysis set[a]/Analysis method (per protocol and SAP)</td>
ITT/ANOVA, ANCOVA[b] 12 week-LOCF, OC	ITT/ANOVA, ANCOVA[b] 12 week-LOCF, OC	ITT/ ANCOVA, 12 week-LOCF, OC	FAS/ANCOVA 12 week-LOCF, OC	FAS/ANCOVA 12 week-LOCF, OC	ITT/ANCOVA 12 week-LOCF, OC	ITT/ANCOVA 16 week-LOCF, OC	ITT/MMRM 12 week, OC

[a]The ITT and FAS analyses were essentially the same; [b]The SAP pre-specified ANOVA, and the protocol pre-specified ANCOVA; AE, adverse event; ANCOVA, analysis of covariance; ANOVA, analysis of variance; FAS, full analysis set; ITT, intent-to-treat; LOCF, last observation carried forward; MMRM, mixed-effects model repeated measures; OC, observed case; PD, Parkinson's disease; SAP, statistical analysis plan; UKPDS, United Kingdom Parkinson's Disease Society.

Supplementary Table 3. Patient disposition

n (%)	6002-US-005		6002-US-006		6002-US-013		6002-0608			6002-009			6002-US-018			6002-EU-007		6002-014		
	Placebo	Istradefylline 40 mg/day	Placebo	Istradefylline 20 mg/day	Placebo	Istradefylline 20 mg/day	Placebo	Istradefylline 20 mg/day	Istradefylline 40 mg/day	Placebo	Istradefylline 20 mg/day	Istradefylline 40 mg/day	Placebo	Istradefylline 20 mg/day	Istradefylline 40 mg/day	Placebo	Istradefylline 40 mg/day	Placebo	Istradefylline 20 mg/day	Istradefylline 40 mg/day
Randomized	66 (100.0)	130 (100.0)	77 (100.0)	163 (100.0)	115 (100.0)	116 (100.0)	119 (100.0)	119 (100.0)	125 (100.0)	126 (100.0)	123 (100.0)	124 (100.0)	154 (100.0)	149 (100.0)	152 (100.0)	152 (100.0)	159 (100.0)	204 (100.0)	202 (100.0)	207 (100.0)
ITT analysis set	66 (100.0)	129 (99.2)	77 (100.0)	163 (100.0)	113 (98.3)	112 (96.6)	118 (99.2)	115 (96.6)	124 (99.2)	123 (97.6)	120 (97.6)	123 (99.2)	146 (94.8)	144 (96.6)	145 (95.4)	151 (99.3)	158 (99.4)	198 (97.1)	194 (96.0)	200 (96.6)
Completed double-blind treatment period	58 (87.9)	114 (87.7)	69 (89.6)	152 (93.3)	103 (89.6)	104 (89.7)	109 (91.6)	106 (89.1)	112 (89.6)	109 (86.5)	111 (90.2)	115 (92.7)	140 (90.9)	131 (87.9)	135 (88.8)	133 (87.5)	147 (92.5)	186 (91.2)	182 (90.1)	178 (86.0)
Discontinued prematurely	8 (12.1)	16 (12.3)	8 (10.4)	11 (6.7)	12 (10.4)	12 (10.3)	10 (8.4)	13 (10.9)	13 (10.4)	17 (13.5)	12 (9.8)	9 (7.3)	14 (9.1)	18 (12.1)	17 (11.2)	19 (12.5)	12 (7.5)	18 (8.8)	20 (9.9)	29 (14.0)
Reason for failure to complete double-blind treatment period[a]																				
Adverse event	5 (7.6)	10 (7.7)	5 (6.5)	6 (3.7)	7 (6.1)	6 (5.2)	2 (1.7)	7 (5.9)	8 (6.4)	6 (4.8)	5 (4.1)	6 (4.8)	7 (4.5)	14 (9.4)	15 (9.9)	10 (6.6)	7 (4.4)	13 (6.4)	10 (5.0)	22 (10.6)
Patient withdrew consent	3 (4.5)	4 (3.1)	1 (1.3)	2 (1.2)	3 (2.6)	0	7 (5.9)	3 (2.5)	4 (3.2)	6 (4.8)	6 (4.9)	3 (2.4)	3 (1.9)	1 (0.7)	1 (0.7)	3 (2.0)	2 (1.3)	3 (1.5)	7 (3.5)	3 (1.4)
Lack of efficacy	0	1 (0.8)	0	1 (0.6)	1 (0.9)	0	-	-	-	-	-	-	1 (0.6)	1 (0.7)	0	3 (2.0)	2 (1.3)	-	-	-
Noncompliance	-	-	-	-	-	-	-	-	-	2 (1.6)	0	0	-	-	-	-	-	0	0	2 (1.0)
Physician's decision	-	-	-	-			1 (0.8)	3 (2.5)	0	2 (1.6)	1 (0.8)	0	-	-	-	-	-	-	-	-
Protocol deviation	0	1 (0.8)	2 (2.6)	2 (1.2)	1 (0.9)	5 (4.3)	-	-	-	1 (0.8)	0	0	1 (0.6)	2 (1.3)	0	1 (0.7)	0	1 (0.5)	0	0
Screen failure	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1 (0.5)	1 (0.5)	1 (0.5)
Death	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	1 (0.5)
Other	-	-	-	-	0	1 (0.9)	-	-	-	-	-	-	2 (1.3)	0	1 (0.7)	2 (1.3)	1 (0.6)	0	2 (1.0)	0

[a]Not all studies captured all discontinuation categories; a dash (-) indicates "not captured"; ITT, intent-to-treat.

Supplementary Table 4 Incidence of select PD- and levodopa/DA-related TEAEs

Adverse Event, n (%)	Placebo	Istradefylline	
		20 mg/day	40 mg/day
8-study pool, n	1010	869	896
Orthostatic hypotension[a]	63 (6.2)	82 (9.4)	66 (7.4)
Falls[b]	77 (7.6)	69 (7.9)	69 (7.7)
Nausea and vomiting[c]	49 (4.9)	56 (6.4)	60 (6.7)
Hallucination[d]	25 (2.5)	27 (3.1)	41 (4.6)
Somnolence (preferred term)	32 (3.2)	28 (3.2)	17 (1.9)
Sleep disturbance[e]	7 (0.7)	19 (2.2)	18 (2.0)
Increased liver enzymes[f]	20 (2.0)	10 (1.2)	22 (2.5)
Impulse control disorder[g]	0	7 (0.8)	5 (0.6)
Neutropenia[h]	3 (0.3)	4 (0.5)	7 (0.8)
Sleep attack[i]	0	1 (0.1)	0
4-study pool, n	426	356	378
Orthostatic hypotension[a]	23 (5.4)	24 (6.7)	26 (6.9)
Falls[b]	40 (9.4)	23 (6.5)	26 (6.9)
Nausea and vomiting[c]	20 (4.7)	17 (4.8)	26 (6.9)
Hallucination[d]	12 (2.8)	8 (2.2)	22 (5.8)
Somnolence (preferred term)	13 (3.1)	15 (4.2)	8 (2.1)
Sleep disturbance[e]	3 (0.7)	3 (0.8)	6 (1.6)
Increased liver enzymes[f]	11 (2.6)	3 (0.8)	7 (1.9)
Impulse control disorder[g]	0	0	1 (0.3)
Neutropenia[h]	0	1 (0.3)	2 (0.5)
Sleep attack[i]	0	1 (0.3)	1 (0.3)

[a]Includes dizziness, orthostatic hypotension, vertigo, dizziness postural, hypotension, blood pressure decreased, vertigo positional, and procedural hypotension.
[b]Includes falls fracture terms (acetabulum fracture, ankle fracture, avulsion fracture, cervical vertebral fracture, clavicle fracture, comminuted fracture, facial bones fracture, fall, femoral neck fracture, femur fracture, foot fracture, forearm fracture, fracture, fractured sacrum, hand fracture, hip fracture, humerus fracture, ilium fracture, lower limb fracture, lumbar vertebral fracture, multiple fractures, patella fracture, pelvic fracture, radius fracture, rib fracture, scapula fracture, spinal compression fracture, spinal fracture, and sternal fracture) and injury terms (accident, contusion, craniocerebral injury, ecchymosis, eyelid injury, face injury, hematoma, head injury, incision site hematoma, injection site hematoma, injury, joint injury, laceration, ligament injury, ligament sprain, limb injury, musculoskeletal injury, periorbital hematoma, skin abrasion, soft tissue injury, tendon injury, and traumatic hematoma).
[c]Includes nausea, procedural nausea, retching, and vomiting.
[d]Includes hallucinations, hallucinations visual, hallucinations olfactory, hallucinations somatic, hallucinations auditory, hallucinations tactile, hallucinations mixed, and illusions.
[e]Includes sleep disorder, irregular sleep phase, poor quality sleep, rapid eye movements, and sleep abnormal.
[f]Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal,

hyperbilirubinemia, jaundice, liver disorder, liver function test abnormal, transaminases increased, urine bilirubin increased, and urobilinogen urine increased.
[g]Includes compulsions, disturbance in sexual arousal, excessive sexual fantasies, gambling disorder, hypersexuality, impulse-control disorder, impulsive behaviour, libido increased, and obsessive-compulsive disorder.
[h]Includes agranulocytosis, granulocytopenia, leukopenia, neutropenia, neutrophil count decreased, neutrophil percentage decreased, pancytopenia, and white blood cell count decreased.
[i]Includes sleep attacks and sudden onset of sleep.

DA, dopamine agonist; PD, Parkinson's disease; TEAE, treatment-emergent adverse event.

Supplementary Figure 1. Summary of Pooled Randomized Clinical Trials
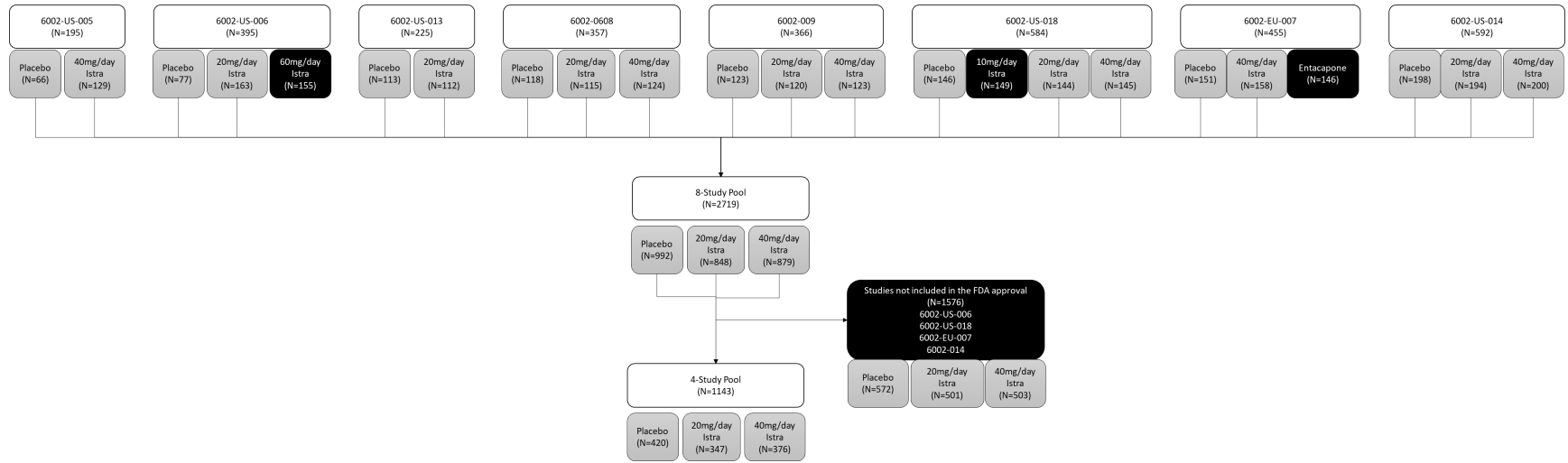
Supplementary File 2: Study narrative for 6002-EU-007 (NCT00199394)

Clinical Study Report Synopsis: 6002-EU-007 (NCT00199394)
Title of Study: A 16-week, Double-Blind, Placebo-Controlled, Randomised, Parallel-Group, Multicentre, International Study to Evaluate the Efficacy and Safety of 40 mg/day KW-6002 (istradefylline) and that of Entacapone versus Placebo as Treatment for Parkinson's Disease in Patients with Motor Response Complications on Levodopa Therapy

Study Period: 24 November 2004 (Date of First Dose) to 03 October 2005 (Date of Last Dose)

Study Centers: A total of 56 centers in the following countries: Argentina; Austria; Chile; Estonia; France; India; Italy; Latvia; Lithuania; Russia; Republic of South Africa; Spain; United Kingdom; and Ukraine.

Clinical Phase: Phase 3

Objectives:

> *Primary Objective*: To establish the efficacy of 40 mg/day istradefylline in reducing the percentage of awake time per day spent in the OFF state in patients with Parkinson's disease (PD) treated with levodopa (LD)*.
> [*Refers throughout this report to LD in combination with either benserazide or carbidopa with or without additional concomitant anti-parkinson medications].

> *Key Secondary Objective*: To evaluate the change in the percentage of ON time without troublesome dyskinesia.

Patients: Consenting patients with PD and motor response complications while receiving LD therapy (n=464) were enrolled internationally at 56 participating centers in Argentina, Austria, Chile, Estonia, France, India, Italy, Latvia, Lithuania, Russia, Republic of South Africa, Spain, United Kingdom, and Ukraine.

Major Inclusion Criteria
- Male or female, 30 years of age or older
- UK Parkinson's Disease Society (UKPDS) brain bank criteria (Step 1 and 2) for PD
- Modified Hoehn and Yahr scale Stage 2 to 4 in the OFF state
- Receiving LD therapy for at least 1 year
- Taking at least 3 doses/day of LD
- Stable PD regimen for at least 4 weeks before baseline
- Predictable end-of-dose wearing-off
- An average of at least 3 h of OFF time per day
- Women of childbearing potential must not be pregnant or lactating and must be using a reliable method of contraception

Major Exclusion Criteria
- Patients who were taking or who had previously taken any COMT inhibitor
- Patients who had had a neurosurgical procedure for PD or who were receiving a centrally active dopamine antagonist
- Patients with a history of psychotic illness or who were receiving an antipsychotic medication within 3 months (or 6 months for depot formulations) before baseline
- Serum ALT or AST >1.5× ULN at screening

- Mini-Mental State Examination (MMSE) ≤25
- History of seizure, seizure disorder, or neuroleptic malignant syndrome
- Patients who had previously received istradefylline
- Patients receiving an investigational medication within 30 days (or 5 half-lives, whichever is longer) before baseline
- Patients receiving any medication disallowed by the protocol

Methodology: Eligible patients were randomized in a 1:1:1 ratio to 1 of the following 3 treatment groups:
- o istradefylline 40 mg/day given with the first daily dose of LD followed by placebo with subsequent doses of LD;
- o entacapone 200 mg to be given with every dose of LD; or
- o placebo to be given with every dose of LD

Following randomization to double-blind treatment, patients entered an initial 4-week period during which their LD dose may have been adjusted to an optimal level if required; however, the frequency of dosing could not have been changed. Patients then entered a 12-week period during which adjustments to the LD dosing regimen were not allowed. Efficacy was evaluated by the 24-h ON/OFF patient diary, Unified Parkinson's Disease Rating Scale (UPDRS), Clinical Global Impression-Severity of Illness scale (CGI-S), Parkinson's Disease Questionnaire-39 (PDQ-39), Medical Outcomes Study 36-item Short Form Health Survey (SF-36), and Patient Global Impression-Improvement (PGI-I) scale. Safety was assessed by physical examinations (including neurological examinations), clinical laboratory tests, 12-lead ECGs, vital signs, body weight, adverse events (AEs), and concomitant medications.

Criteria for Evaluation
Efficacy:
Primary Efficacy Measurement: Change from baseline in the percentage of awake time per day spent in the OFF state at Endpoint (Week 16 value or the last available post-baseline value at the time of premature discontinuation from the study)
Secondary Efficacy Measurements: Actual values and changes from baseline in:
1. Based on the patient's valid 24-h ON/OFF Patient Diary, using the home diary developed by RA Hauser et al., 2000 [1]
   OFF State:
   - Percentage and total hours of awake time per day spent in the OFF state at Weeks 2, 4, 6, 8, 12, and 16 (including actual values for percentage at Endpoint)
   - Percentage and total hours of awake time per day spent in the ON state at Weeks 2, 4, 6, 8, 12, 16, and Endpoint, for:
   ON States: Without Dyskinesia, With Dyskinesia, With Non-troublesome Dyskinesia, With Troublesome Dyskinesia, and Without Troublesome Dyskinesia (defined as the sum of the awake time per day spent in the ON state without dyskinesia plus the awake time per day spent in the ON state with non-troublesome dyskinesia):
2. Based on UPDRS measured at Weeks 2, 4, 6, 8, 12, 16, and Endpoint
   - UPDRS Subscale I score (Mentation, Behavior, and Mood) in the ON state;
   - UPDRS Subscale II score (Activities of Daily Living) in the ON state and in the OFF state;
   - UPDRS Subscale III score (Motor Examination);
   - UPDRS Subscale I to III total score;
   - UPDRS Subscale II to III total score;
   - UPDRS Subscale IVA score.
3. Based on CGI-S at Weeks 2, 4, 6, 8, 12, 16, and Endpoint
4. Based on PDQ

- PDQ-39 total score and subscale scores at Weeks 4, 16, and Endpoint; and
- PDQ-8 score at Weeks 4, 16, and Endpoint
5. Based on SF-36 summary scores and subscales at Weeks 4, 16, and Endpoint
6. Based on Patient Global Impression (actual values only) at Weeks 2, 4, 6, 8, 12, 16, and Endpoint

Safety: AEs, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs, weight, physical and neurological examination findings, and 12-lead ECGs

Statistical Methods:
All efficacy analyses were carried out based on the intent-to-treat (ITT) analysis set.

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

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

The sample size per treatment group for testing the primary efficacy variable was based on the expected difference in change from baseline in the percentage of awake time per day spent in the OFF state at Endpoint between the 40 mg/day istradefylline treatment group and placebo. A sample size of 130 patients 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 patients who were not expected to qualify for the ITT analysis set (e.g., fewer than 4%), approximately 135 patients were to be randomized to each treatment group, giving a total of 405 patients. 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.

SUMMARY OF RESULTS
Subject Disposition:
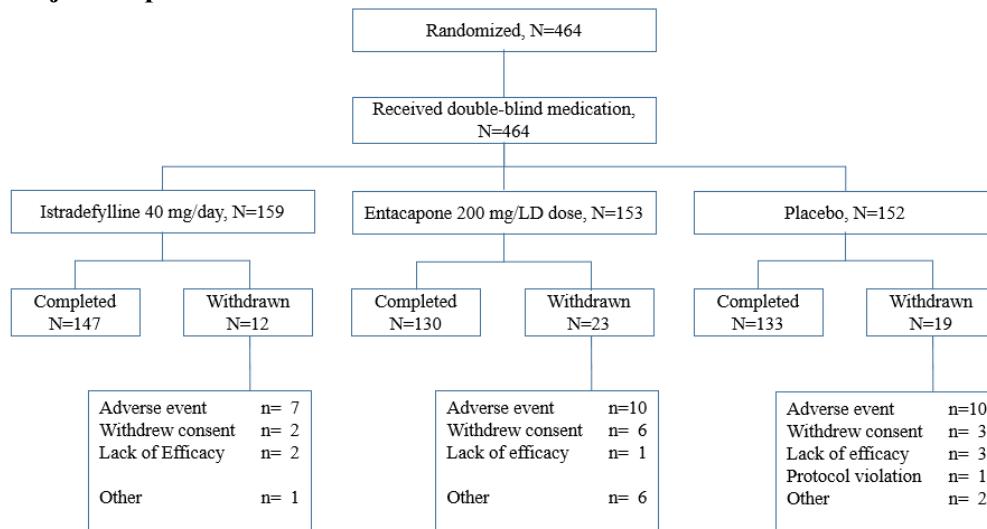
LD, levodopa.

Demographic and Baseline Characteristics: Demographic characteristics and PD history were similar among the 3 treatment groups. The 3 treatment groups were similar at baseline for the primary and secondary efficacy variables.

Demographic and other baseline characteristics (safety analysis set)

Demographic characteristic		Placebo n=152	Istradefylline 40 mg/day n=159	Entacapone 200 mg/LD dose n=153	Total N=464
Age (y)	Mean (SD)	62.4 (8.60)	60.8 (9.29)	61.3 (10.24)	61.5 (9.41)
Sex (male)	n (%)	92 (60.5)	99 (62.3)	93 (60.8)	284 (61.2)
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 (mixed ancestry)		2 (1.3)	2 (1.3)	3 (2.0)	7 (1.5)
Height (cm)	Mean (SD)	166 (9.6)	166 (10.1)	167 (9.6)	166 (9.7)
Weight, at screening (kg)	Mean (SD)	69 (13.0)	71 (15.1)	70 (14.1)	70 (14.2)
Current smoker [yes]	n (%)	9 (5.9)	8 (5.0)	7 (4.6)	24 (5.2)

LD, levodopa; SD, standard deviation.

PD history at baseline (safety analysis set)

Characteristic	Placebo n=152	Istradefylline 40 mg/day n=159	Entacapone 200 mg/LD dose n=153	Total N=464
Time since diagnosis (y)				
n	152	158	153	463
Mean (SD)	8.9 (4.72)	8.1 (3.90)	7.9 (4.50)	8.3 (4.39)
Time since initiation of LD (y)				
n	151	157	153	461
Mean (SD)	7.5 (4.32)	6.9 (3.86)	7.1 (4.37)	7.2 (4.18)
Mean daily LD dose [a] (mg)				
n	152	159	153	464
Mean (SD)	650 (344.2)	608 (303.2)	635.4 (308.9)	631 (318.9)
Time since onset of motor complications (y)				
n	151	158	153	462
Mean (SD)	3.0 (2.81)	3.0 (2.38)	3.2 (3.17)	3.1 (2.79)

[a]ITT analysis set; ITT, intent-to-treat; LD, levodopa; SD, standard deviation.

PD characteristics at baseline (safety analysis set)

Characteristic	Placebo n=152	Istradefylline 40 mg/day n=159	Entacapone 200 mg/LD dose n=153	Total N=464
CGI-S: Moderately, markedly, or severely ill				
% of patients	80.3%	78.6%	81.0%	80.0%
MMSE score				
Mean (SD)	28.6 (1.34)	28.8 (1.24)	28.7 (1.30)	28.7 (1.30)
Modified Hoehn & Yahr scale Stage 3 or 4				
% of patients	53.9%	50.3%	54.2%	52.8%

CGI-S, Clinical Global Impression-Severity of Illness scale; MMSE, Mini-Mental State Examination; SD, standard deviation.

Study Drug Exposure: The median duration of exposure was 16.0 weeks (range, 0.3 to 18.6) for all treatment groups. Overall, 86% of patients completed >13 to ≤17 weeks of double-blind treatment (placebo, 84%; istradefylline, 91%; entacapone, 83%).

Efficacy Results:
The conclusions are based on the efficacy analyses of the ITT analysis set (455 patients).

Efficacy endpoints (ITT analysis set)

Endpoint		Placebo n=151	Istradefylline 40 mg/day n=158	Entacapone 200 mg/LD dose n=146
Primary endpoint: Change from baseline in percentage of awake time spent in the OFF state				
Baseline	mean (SD)	41.5 (12.26)	38.6 (11.63)	40.1 (13.42)
Endpoint	mean (SD)	36.7 (17.31)	34.3 (16.10)	32.6 (17.74)
Change from baseline to Endpoint	LS mean [95% CI]	-4.53 [-7.02, -2.04]	-5.14 [-7.58, -2.69]	-7.82 [-10.34, -5.30]
Difference from placebo	LS mean [95% CI]		-0.61 [-4.05, 2.83]	-3.29 [-6.77, 0.19]
	p value		0.729	0.064
Secondary endpoint[a]: Change from baseline in hours/day spent in the OFF state				
Baseline	mean (SD)	6.61 (2.13)	6.15 (2.05)	6.47 (2.38)
Endpoint	mean (SD)	5.88 (2.95)	5.52 (2.74)	5.28 (2.95)

Endpoint		Placebo n=151	Istradefylline 40 mg/day n=158	Entacapone 200 mg/LD dose n=146
Change from baseline to Endpoint	LS mean	-0.70	-0.77	-1.22]
Difference from placebo	LS mean		-0.07	-0.52
Secondary endpoint[a]: LS mean difference vs placebo in the change from baseline in hours/day spent in the ON state, by ON state characteristic				
ON without dyskinesia			-0.23	0.00
ON with dyskinesia			0.53	0.74[b]
ON with non-troublesome dyskinesia			0.21	0.37
ON with troublesome dyskinesia			0.25	0.35[c]
ON without troublesome dyskinesia			-0.03	0.36
Secondary endpoint[a]: LS mean difference vs placebo in the change from baseline in UPDRS subscale scores				
Part I (ON)			-0.2	-0.2
Part II (ON)			-0.6	-0.6
Part II (OFF)			-0.4	-1.2[d]
Part III (ON)			-1.6	-1.8[e]
Parts I to III (Total ON + OFF)			-2.7	-3.8[f]
Part IVA (ON)			0.0	0.2
Secondary endpoint[a]: LS mean difference vs placebo in the change from baseline in scores for other scales				
CGI-S			-0.1	-0.1
PDQ-39			-0.23	-1.15
PDQ-8			-0.47	-1.09
SF-36 [physical components summary score]			0.72	1.97[g]
SF-36 [mental health components summary score]			1.26	0.74
PGI-I [overall condition score]				

Endpoint	Placebo n=151	Istradefylline 40 mg/day n=158	Entacapone 200 mg/LD dose n=146
% with moderate improvement	14.6	19.0	24.7[h]
% with mild improvement	31.1	36.7	34.9[h]
% with no change from baseline	33.8	30.4	22.6[h]
% with mild deterioration	14.6	7.6	11.0[h]
% with moderate deterioration	6.0	6.3	6.8[h]

For all primary and secondary variables (except PGI-I), the pairwise *p* value was based on LS means from main effects ANCOVA with terms for baseline, Investigator, and treatment. For the PGI-I, 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. [a]All LS mean differences from placebo were not significant (ie, $p>0.05$), except as noted; [b]$p=0.012$; [c]$p=0.029$; [d]$p=0.016$; [e]$p=0.043$; [f]$p=0.007$; [g]$p=0.008$; [h]$p=0.044$; ANCOVA, analysis of covariance; CGI-S, Clinical Global Impression-Severity of Illness; CI, confidence interval; ITT, intent-to-treat; LD, levodopa; LS, least-squares; PDQ-8, Parkinson's Disease Questionnaire-sum of questions 7, 12, 17, 25, 27, 31, 35, and 37; PDQ-39, Parkinson's Disease Questionnaire-sum of questions 1 to 39; PGI-I, Patient Global Impression-Improvement; SD, standard deviation; SF-36, Medical Outcomes Study 36-item Short Form Health Survey; UPDRS, Unified Parkinson's Disease Rating Scale.

Safety Results: The conclusions based on the safety analysis set (464 patients) are as follows:

Study drug was well-tolerated in all patients who were randomized and received at least 1 dose of study drug. The percentages of patients who completed the 16-week double-blind period were 92.5% in the istradefylline group, 85.0% in the entacapone group, and 87.5% in the placebo group.

AEs: The overall incidence of treatment-emergent adverse events (TEAEs) was similar in all three treatment groups: 103 (64.8%) patients in the istradefylline group, 101 (66.0%) in the entacapone group, and 97 (63.8%) patients in the placebo group.

Non-Serious AEs
- The most frequently reported treatment-emergent AEs (TEAEs) in the istradefylline group were dyskinesia, tremor, and back pain. Dyskinesia was reported in 22 (13.8%) patients in the istradefylline group, 20 (13.1%) patients in the entacapone group, and 11 (7.2%) patients in the placebo group. Tremor was reported for 10 (6.3%) patients in the istradefylline group, 5 (3.3%) patients in the entacapone group, and 7 (4.6%) patients in the placebo group. Back pain was reported for 10 (6.3%) patients in the istradefylline group and in 4 (2.6%) patients in each of the entacapone and placebo groups. The TEAE worsening symptoms of PD was reported more frequently in the placebo group (11.2%) than in the istradefylline (5.7%) or the entacapone (7.2%) groups.
- The incidence of patients with a TEAE that was considered by an Investigator as related to study drug was 42.8% (68 patients) in the istradefylline group, 46.4% (71 patients) in the entacapone group, and 47.4% (72 patients) in the placebo group.
- The most frequently reported TEAE considered possibly or probably related to study drug was dyskinesia, which was reported by 21 (13.2%) patients in the istradefylline group, 20 (13.1%) patients in the entacapone group, and 11 (7.2%) patients in the placebo group.
- The number of patients with TEAEs that were considered severe was similar in each treatment group. A total of 40 (8.6%) patients experienced 90 severe TEAEs: 13 (8.2%) patients with 26 events in the istradefylline group, 13 (8.5%) patients with 33 events in the entacapone group, and 14 (9.2%)

patients with 31 events in the placebo group. The number of patients with severe dyskinesia in the istradefylline and placebo groups was the same (ie, 2 [1.3%] patients in each group). In the entacapone group, 3 (2.0%) patients experienced severe dyskinesia.
- Three deaths were reported during the study: 1 death ("severe pneumonia" and "muscle rigidity" AEs) in the placebo group and 2 deaths ("acute respiratory distress" and "heat stroke" AEs) in the entacapone group. The death in the placebo group was considered by the Investigator as related to study drug treatment, and the 2 deaths in the entacapone group were considered unrelated to study drug treatment.

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

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

Clinical Laboratory Evaluations, Vital Signs, Physical and Neurological Examination Findings, and ECG Findings:
- Approximately 20% of patients had a potentially clinically significant (PCS) laboratory value; the incidence was similar in all groups, with no relevant trends in the type of PCS laboratory value observed.
- No clinically important differences were observed between the istradefylline and placebo groups for changes in clinical laboratory assessments, vital signs (sitting blood pressure and pulse rate), physical or neurological examinations, or ECGs.

Discussion:
The absence of statistical separation of istradefylline from placebo in the reduction in percentage of time spent in the OFF state in this study may have been due to a statistically significant treatment-by-center interaction (p=0.008, based on the prespecified 2-sided alpha=0.100 level). In addition, the internal validity of this study was not established, as there was no statistical separation of entacapone from placebo for the primary endpoint. The lack of assay sensitivity could be associated with the lack of statistical separation between istradefylline and placebo for the primary endpoint. Furthermore, examination of the treatment-by-center results showed a qualitative interaction at some centers where placebo performed better than entacapone, supporting the absence of assay sensitivity.

The study may have failed for methodologic reasons since entacapone treatment cannot be fully blinded because of the entacapone-specific AE of urine discoloration. Furthermore, the effect of entacapone in this study was smaller than might have been expected: -3.29%, corresponding to -0.52 h/day, relative to placebo (p=0.081). In a pooled analysis of entacapone trials [2], entacapone reduced OFF time, relative to placebo, by 0.8 h/day, and in a recent meta-analysis of entacapone trials [3], the overall reduction in OFF time was -0.98 h/day (range, -0.32 to -1.60 h/day).

Conclusions:
No significant decrease in percentage of time spent in the OFF state for the istradefylline-treated group versus placebo was observed. Nevertheless, this study demonstrated that oral istradefylline at 40 mg/day in combination with LD and other dopaminergic anti-parkinson medications showed a numerical

improvement in motor function as demonstrated by the Motor Subscale of the UPDRS. There were fewer reports of the TEAE worsening symptoms of PD in istradefylline-treated patients than in those receiving placebo. Istradefylline was well-tolerated in this patient population, with a safety profile similar to placebo.

References

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[2] Kuoppamäki M, Vahteristo M, Ellmén J, Kieburtz K (2014) Pooled analysis of phase III with entacapone in Parkinson's disease. *Acta Neurol Scand* **130**, 239-247.

[3] Li J, Lou Z, Liu X, Sun Y, Chen J (2017) Efficacy and safety of adjuvant treatment with entacapone in advanced Parkinson's disease with motor fluctuation: a systematic meta-analysis. *Eur Neurol* **78**, 143-53.

Supplementary File 3. Study narrative for 6002-014 (NCT01968031) **Clinical Study Report Synopsis: 6002-014 (NCT01968031)**

Title of Study: 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 Patients with Moderate to Severe Parkinson's Disease

Study Period: 05 November 2013 (Date of First Patients Enrolled) to 23 September 2016 (Date of Last Visit)

Study Centers: A total of 88 centers in the following countries: Canada, Czech Republic, Germany, Israel, Italy, Poland, Serbia, and USA.

Clinical Phase: Phase 3

Objectives: The study's population reflected maximally and optimally treated patients with Parkinson's disease (PD) experiencing motor fluctuations and dyskinesia on levodopa (LD) therapy. Therefore, the patients examined in this study were essentially a very strictly circumscribed refractory PD population.

> _**Primary Objective:**_ To establish the efficacy of istradefylline 20 and 40 mg/day in reducing the total hours of OFF time/day in patients with moderate to severe PD with motor fluctuations and dyskinesia on LD combination therapy (LD/carbidopa or LD/benserazide).

> _**Key Secondary Objective:**_ To evaluate the change from baseline in the total hours of ON time/day without troublesome dyskinesia.

Patients: Consenting patients with moderate to severe PD and chronic LD-related motor fluctuations and dyskinesia (n=613) were enrolled internationally at 88 participating centers in Canada, Czech Republic, Germany, Israel, Italy, Poland, Serbia, and USA.

**Major Inclusion Criteria**
- Male or female, 30 years of age or older
- UK Parkinson's Disease Society (UKPDS) brain bank criteria (Step 1 and 2) for PD
- Modified Hoehn and Yahr scale Stage 2 to 4 in the ON state
- Receiving LD therapy for at least 1 year with beneficial clinical response at the baseline visit
- Stable dopaminergic regimen for at least 4 weeks immediately prior to randomization
- Taking at least 400 mg LD combination therapy daily and on stable regimen of any other anti-parkinson drugs (MAO-B inhibitor, COMT inhibitor, dopamine agonist [DA]) for at least 2 weeks prior to randomization
- Documented end-of-dose wearing-off and LD-induced dyskinesia
- An average of at least 2 h of OFF time per day
- Women of childbearing potential must not be pregnant or lactating and must be using a reliable method of contraception

**Major Exclusion Criteria**
- Patients on apomorphine and/or dopamine receptor antagonists or direct gastrointestinal LD infusion
- Patients receiving only anticholinergic medications or amantadine for treatment of PD symptoms
- Patients who had had a neurosurgical procedure for PD

- Patients with hepatic impairment (Child-Pugh category A, B, or C)
- Patients taking an adenosine A_{2A} antagonist, potent CYP3A4 inhibitors, or potent CYP3A4 inducers
- Patients who smoke >5 cigarettes/day

Study Design/Methodology

Eligible patients were randomized (1:1:1) to 12 weeks of double-blind treatment with istradefylline 20 mg/day, 40 mg/day, or matching placebo, followed by a 30-day safety follow-up period for patients who terminated from the study early. Following randomization to double-blind treatment, patients were evaluated for efficacy by at least one valid 24-h ON/OFF patient diary, the Unified Parkinson's Disease Rating Scale (UPDRS), the Montreal Cognitive Assessment (MoCA), Beck Depression Inventory (BDI), and the Patient Global Impression-Improvement scale (PGI-I). Electronic diaries were utilized to facilitate data capture. Three 24-h ON/OFF patient diaries were completed on 3 consecutive days immediately prior to the baseline visit. Visits were to occur in the ON state.

Safety was assessed by physical examinations, clinical laboratory tests, and 12-lead electrocardiogram (ECG) at screening, at baseline, and at selected, subsequent scheduled visits. Vital signs (including orthostatic blood pressure and heart rate), weight, concomitant medications, and adverse events (AEs) were assessed at every visit throughout the study. The Columbia-Suicide Severity Rating Scale (C-SSRS) was completed at baseline, at every study visit, and Week 12 (or at early termination [ET]), and the Epworth Sleepiness Scale (ESS) and Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS) were completed at baseline, Week 6, and Week 12 (or at ET). Decreases in LD combination therapy due to LD-related AEs were permitted at the investigator's discretion and recorded. However, the LD dosing interval was not to be changed, if possible. No increase in the LD regimen was permitted.

Criteria for Evaluation
Efficacy:
  Primary Efficacy Measurement: Change from baseline in total hours/day spent in the OFF state

  Secondary Efficacy Measurements: Change from screening/baseline (as appropriate) in:
  - Total hours of ON time/day without troublesome dyskinesia (key secondary variable)
  - UPDRS Motor Examination (Part III)
  - UPDRS Activities of Daily Living score (Part II)
  - UPDRS Mentation, Behavior, and Mood (Part I)
  - Total UPDRS (Parts I+II+III)
  - PGI-I
  - Sleep time in hours per day based on 24-h diaries
  - Percentage of awake time spent in the OFF state
  - Percentage of ON time/day without troublesome dyskinesia
  - Total hours and percentage of ON time/day (without dyskinesia, with dyskinesia, with non-troublesome dyskinesia, and with troublesome dyskinesia)
  - MoCA
  - BDI

  Safety: AEs; clinical laboratory tests (chemistry, hematology, and urinalysis) and serum/urine pregnancy tests; vital signs (including orthostatic blood pressure and pulse rate) and weight; 12-lead ECG; complete medical history, physical examination; C-SSRS since last visit; ESS; and QUIP-RS

Statistical Methods:

The total hours in any particular state for a visit were calculated as the average across all valid diaries collected that week, ie, as the average of 1, 2, or 3 valid diaries. If all three completed diaries within the same week were invalid, then the overall diary entry for that week was considered missing. The change from baseline in total hours and change from baseline in percentage of awake time/day spent in the OFF state were then calculated. The total hours and percentage of awake time per day spent in the ON state (without dyskinesia, with dyskinesia, with non-troublesome dyskinesia, and with troublesome dyskinesia) and asleep were calculated following the same algorithm as for the OFF state variables.

For the calculation of UPDRS subscale scores (for Parts I, II, III, and total), when at least one individual component score is missing, the subscale score was set to missing.
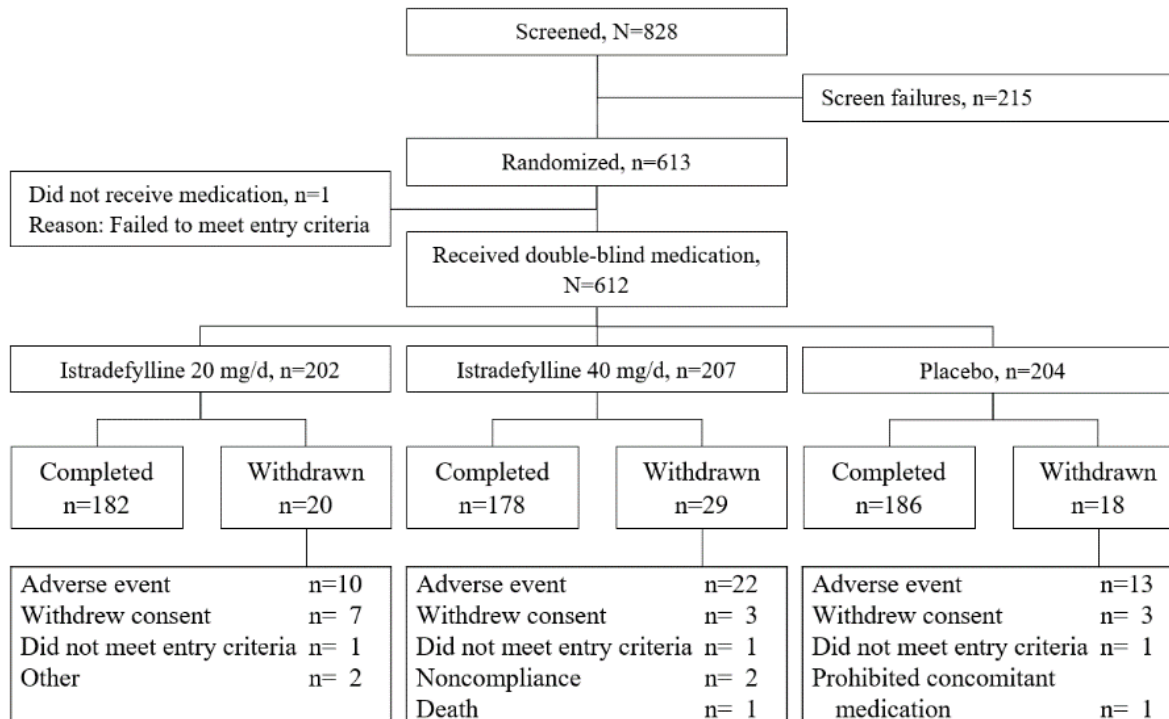
The primary efficacy analysis and analysis of secondary endpoints were based on the intent-to-treat (ITT) analysis set. The primary efficacy variable was analyzed using a mixed-model repeated-measures (MMRM) approach with baseline value as a covariate; fixed-effect terms in the model for study site, treatment group, week, and treatment-by-week interaction; and an unstructured covariance matrix. Using this model, the difference in the change from baseline in total hours OFF time between the 40 mg/day treatment group and the placebo treatment group was tested using a t-test at the two-sided 5% significance level. In the event that the unstructured covariance matrix was non-estimable (due to lack of convergence) when fitting the MMRM to the observed study data, an autoregressive model 1 (AR1) covariance matrix was used instead.

A simple hierarchical sequence of statistical testing was used for the primary efficacy variable and the key secondary efficacy variable (total hours of ON time per day without troublesome dyskinesia) for both istradefylline doses using a two-sided test at a critical alpha of 0.05 as follows: Step 1, Change from baseline to Week 12 in total OFF time for 40 mg/day versus placebo; Step 2, Change from baseline to Week 12 in total OFF time for 20 mg/day versus placebo; Step 3, Change from baseline to Week 12 in total ON time without troublesome dyskinesia for 40 mg/day versus placebo; Step 4, Change from baseline to Week 12 in total ON time without troublesome dyskinesia for 20 mg/day versus placebo. All continuous supportive and secondary efficacy variables were analyzed using this same MMRM.

A sample size of 185 patients for each treatment group provided 90% power to detect a difference with an effect size of 0.8 h (48 min) between the 40 mg/day treatment group and the placebo treatment group at the one-sided 2.5% significance level. The test used was based on an MMRM with 4 post-baseline measurements with the standard deviation within patients of 2.7 h. This power calculation extended to a 3-arm MMRM assuming that the istradefylline 20 mg/day group had a change from baseline value between those of the placebo and istradefylline 40 mg/day groups. To account for potential dropouts, the required sample size of 185 patients per treatment group was increased by 9.5% (approximately 18 patients) based on the dropout rate for previous istradefylline studies. The total sample size used for this study was planned as 609 patients, with 203 patients per treatment group.

SUMMARY OF RESULTS
Subject Disposition:

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                        ┌─────────────────────┐
                        │  Screened, N=828    │
                        └─────────┬───────────┘
                                  │              ┌──────────────────────────┐
                                  ├──────────────│  Screen failures, n=215  │
                                  │              └──────────────────────────┘
                        ┌─────────┴───────────┐
                        │  Randomized, n=613  │
 ┌───────────────────────────────┐ │
 │ Did not receive medication, n=1│ │
 │ Reason: Failed to meet entry   ├─┤
 │ criteria                       │ │
 └───────────────────────────────┘ │
                        ┌───────────┴──────────────────────┐
                        │ Received double-blind medication, │
                        │            N=612                  │
                        └───────────────────────────────────┘
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┌──────────────────────────┐  ┌──────────────────────────┐  ┌──────────────────────┐
│ Istradefylline 20 mg/d,  │  │ Istradefylline 40 mg/d,  │  │  Placebo, n=204      │
│        n=202             │  │        n=207             │  │                      │
└──────────────────────────┘  └──────────────────────────┘  └──────────────────────┘
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Completed n=182	Withdrawn n=20	Completed n=178	Withdrawn n=29	Completed n=186	Withdrawn n=18

	Withdrawn n=20		Withdrawn n=29		Withdrawn n=18
Adverse event	n=10	Adverse event	n=22	Adverse event	n=13
Withdrew consent	n= 7	Withdrew consent	n= 3	Withdrew consent	n= 3
Did not meet entry criteria	n= 1	Did not meet entry criteria	n= 1	Did not meet entry criteria	n= 1
Other	n= 2	Noncompliance	n= 2	Prohibited concomitant medication	n= 1
		Death	n= 1		

A total of 828 patients were screened for participation in this study, with 613 patients randomly assigned to receive study drug: 202 patients randomized to istradefylline 20 mg/day, 207 patients randomized to istradefylline 40 mg/day, and 204 patients randomized to placebo. Of those randomized, 612 patients (99.8%) received at least 1 dose of study drug, and 546 patients (89.1%) completed the 12-week double-blind treatment period. Overall, 67 (10.9%) patients prematurely discontinued from the study: 20 (9.9%) in the istradefylline 20 mg/day group, 29 (14.0%) in the istradefylline 40 mg/day group, and 18 (8.8%) in the placebo group. The most frequent reason for premature discontinuation was AEs for 45 (7.3%) of patients overall: 5.0% of patients receiving istradefylline 20 mg/day, 10.6% of patients receiving istradefylline 40 mg/day, and 6.4% of patients receiving placebo.
Demographic and other baseline characteristics (safety analysis set)

Demographic characteristic		Placebo n=204	Istradefylline		Total N=612
			20 mg/day n=201	40 mg/day n=207	
Age (y)	Mean (SD)	63.8 (8.49)	63.5 (8.65)	64.5 (8.17)	63.9 (8.43)
Sex (male)	n (%)	124 (60.8)	125 (62.2)	126 (60.9)	375 (61.3)
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/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 (9.9)	171 (9.8)	171 (9.2)	171 (9.6)
Weight, at screening (kg)	Mean (SD)	78 (15.7)	81 (16.4)	79 (17.0)	79 (16.4)
Current smoker [yes]	n (%)	5 (2.5)	12 (6.0)	9 (4.3)	26 (4.2)
Cigarettes smoked/day, ≤5	n (%)	5 (2.5)	12 (6.0)	9 (4.3)	26 (4.2)
Cups[a]/day caffeinated beverage mean (SD)		1.5 (1.37)	1.5 (1.45)[b]	1.4 (1.26)	1.5 (1.36)[c]

[a]8 ounces/cup; [b]n=200; [c]n=611; SD=standard deviation.

All baseline demographic characteristics in the safety analysis set were similar among the istradefylline 20 mg/day, istradefylline 40 mg/day, and placebo groups. Approximately two-thirds (61.3%) of the patients were male, and the majority (96.6%) were Caucasian. The mean age was 64 years. At baseline, only 4.2% were smokers (≤ 5 cigarettes/day), and the population averaged a median of 1.0 eight-ounce cups (range, 0 to 12 cups) of caffeinated beverages each day.

Study Drug Exposure: The median duration of exposure was 12.1 weeks for all treatment groups (range, 0.1 to 15.1 weeks. At least 78% (77.8% to 83.1%) of patients in each treatment group completed between 10 and 12 weeks of double-blind treatment.

PD history and baseline characteristics (safety analysis set)

Characteristic		Placebo n=204	Istradefylline		Total N=612
			20 mg/day n=201	40 mg/day n=207	
Time since diagnosis (y)	n (%)				
<1		0	0	0	0
1 - 3		7 (3.4)	10 (5.0)	9 (4.3)	26 (4.2)
4 - 7		66 (32.4)	76 (37.8)	66 (31.9)	208 (34.0)
≥8		131 (64.2)	115 (57.2)	132 (63.8)	378 (61.8)
Time since initiation of LD (y)					
n		204	201	206	611
Mean (SD)		8.9 (4.03)	8.5 (4.58)	8.9 (4.58)	8.8 (4.40)
Mean daily LD dose (mg)					
n		204	201	207	612
Mean (SD)		815 (385.0)	835 (360.8)	842 (394.4)	831 (380.1)

Characteristic	Placebo n=204	Istradefylline 20 mg/day n=201	40 mg/day n=207	Total N=612
Time since onset of motor complications (y)				
n	203	200	204	607
Mean (SD)	6.1 (4.32)	5.7 (3.98)	6.3 (4.39)	6.0 (4.23)
Total hours/day spent in the OFF state				
n	204	201	207	612
Mean (SD)	5.4 (2.02)	5.4 (1.98)	5.2 (2.08)	5.3 (2.02)
Percentage of awake time/day spent in the OFF state				
n	204	201	207	612
Mean (SD)	34.4 (12.25)	33.7 (11.95)	33.0 (12.81)	33.7 (12.34)
Total hours/day in the ON State without troublesome dyskinesia				
n	204	201	207	612
Mean (SD)	9.3 (2.59)	9.7 (2.31)	9.7 (2.38)	9.5 (2.43)
Mean UPDRS scores (SD)				
n	204	201	206	611
UPDRS - Part I	1.8 (1.70)	1.3 (1.26)	1.6 (1.46)	1.6 (1.49)
UPDRS - Part II	12.2 (5.23)	12.0 (5.65)	13.2 (5.83)	12.5 (5.59)
UPDRS - Part III	21.8 (10.76)	22.7 (11.52)	23.4 (12.03)	22.6 (11.45)
UPDRS - Total Score	35.7 (14.74)	36.1 (15.87)	38.2 (16.57)	36.7 (15.76)

LD, levodopa; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

Efficacy Results

Primary Endpoint: At Week 12, the least-squares (LS) mean changes from baseline in the hours/day spent in the OFF state were -0.88, -1.20, and -1.15 for the placebo, istradefylline 20 mg/day and 40 mg/day groups, respectively. The differences in the LS mean changes [95% CI] between the istradefylline 20 mg/day and 40 mg/day groups and placebo were -0.32 [-0.76, 0.12] and -0.27 [-0.70, 0.17] hours/day, respectively. The t-test from the MMRM analysis did not show a statistically significant difference in changes from baseline to Week 12 between the istradefylline 20 mg/day or 40 mg/day dose groups and the placebo group in the total hours/day spent in the OFF state (primary efficacy endpoint, p=0.156 and p=0.234, respectively). However, there were consistent numerical decreases in OFF time for both istradefylline treatment groups over time, and the mean total hours of OFF time were consistently less than placebo.

At Week 2, the LS mean changes from baseline in hours/day spent in the OFF state were -0.50, -0.78, and -0.96 for the placebo, istradefylline 20 mg/day and 40 mg/day groups, respectively. The differences in the LS mean changes [95% CI] between the istradefylline 20 mg/day and 40 mg/day groups and placebo were -0.28 [-0.63, 0.06] and -0.46 [-0.79, -0.12] hours/day, respectively. At Week 10, the LS mean changes from baseline in hours/day spent in the OFF state were -0.91, -1.31, and -1.40 for the placebo, istradefylline 20 mg/day and 40 mg/day groups, respectively. The differences in the LS mean changes [95% CI] between the istradefylline 20 mg/day and 40 mg/day groups and placebo were -0.40 [-0.81, 0.01] and -0.49 [-0.89, -0.08] hours/day, respectively (p=0.057 and p=0.020, respectively).

Key Secondary Endpoint: At Week 12, the LS mean changes from baseline in hours/day spent in the ON state without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia) were 0.77, 1.01, and 0.77 for the placebo, istradefylline 20 mg/day and 40 mg/day groups, respectively. The differences in the LS mean changes [95% CI] between the istradefylline 20 mg/day and 40 mg/day groups and placebo were 0.24 [-0.28, 0.77] and 0.00 [-0.52, 0.53] hours/day, respectively. The t-test from the MMRM analysis did not show a statistically significant difference in change from baseline to Week 12 between the istradefylline 20 mg/day or 40 mg/day dose groups and the placebo group (p=0.366 and 0.986, respectively) in total hours/day spent in the ON state without troublesome dyskinesia. The observed change from baseline was numerically greater for the istradefylline 20 mg/day group than placebo starting at Week 6 (1.06 versus 0.88, respectively); the change from baseline for the istradefylline 40 mg/day group was similar to placebo (0.74 versus 0.88, respectively).

Other Secondary Endpoints: The t-test from the MMRM analysis did not show a statistically significant difference in changes from baseline to Week 12 between the istradefylline 20 mg/day or 40 mg/day dose groups and the placebo group in any of the analyses of ON time, UPDRS scores, PGI-I, sleep, percentages of awake time/day spent in the OFF state, MoCA, or BDI. At Week 12, the LS mean changes in both MoCA and BDI for each group were similar and minimal (MoCA: -0.1, -0.1, and -0.2; BDI: -1.2, -1.3, and -1.0; for the placebo, istradefylline 20 and 40 mg/d groups, respectively), indicating no adverse changes in cognition or depression.

Safety Results: Of the 612 patients who received study drug, the incidence of any treatment-emergent AEs (TEAEs) regardless of relationship to study drug was similar for the placebo, istradefylline 20 mg/day, and 40 mg/day groups (55.9%, 58.7%, and 64.7%, respectively).

AEs: The most frequently reported TEAE was dyskinesia, reported in 6.9%, 11.4%, and 16.4% of patients in the placebo, istradefylline 20 mg/day, and istradefylline 40 mg/day groups, respectively. TEAEs reported in at least 5% of patients in any treatment group included fall (4.4%, 6.5%, 8.7%), nausea (1.5%, 4.0%, and 5.8%) and insomnia (2.5%, 5.0%, and 3.4%) for placebo, istradefylline 20 mg/day, and 40 mg/day, respectively. The most frequently reported treatment-related TEAE (≥5% of patients in any treatment group) was dyskinesia in 5.9%, 10.0%, and 16.4% of patients in the placebo, istradefylline 20 mg/day, and istradefylline 40 mg/day groups, respectively.

Other Significant Adverse Events: A total of 44 patients discontinued treatment because of TEAEs: 13 (6.4%), 10 (5.0%), and 21 (10.1%) patients in the placebo, istradefylline 20 mg/day, and 40 mg/day groups, respectively.

Serious Adverse Events (SAEs): One subject (istradefylline 40 mg/day) died from acute cardiac failure during the study. The event was considered unlikely to be related to study drug by the Investigator. A total of 21 patients experienced treatment-emergent SAEs during the study: 7 (3.4%), 6 (3.0%), and 8 (3.9%) patients in the placebo, istradefylline 20 mg/day, and istradefylline 40 mg/day groups, respectively. All SAE terms were single occurrences, and there were no trends in types of SAEs reported. Most of the SAEs were considered either not related or unlikely to be related to study drug by the Investigators. Five patients experienced treatment-related SAEs: confusional state and edema in one patient; congestive cardiac failure and pneumonia in another patient; vertigo in a third patient; constipation in a fourth patient; and increased ALT, increased AST, increased LDH, and increased CPK in a fifth patient.

Clinical Laboratory Measurements, Vital Signs, Physical Examinations, ECG, C-SSRS, ESS, and QUIP-RS Findings: No clinically relevant differences were observed between groups for changes in clinical laboratory assessments, vital signs (sitting blood pressure and pulse rate), physical examinations, ECGs, or neurological examinations. The incidence of suicidal ideation and behavior per the C-SSRS

decreased while receiving study drug through Week 12. There was no meaningful change from baseline in daytime sleepiness per the ESS Total Score. Istradefylline was not shown to be causative of thoughts, urges/desires, and behaviors associated with impulse control disorders per the QUIP-RS Impulsive-Compulsive Disorder Total Score.

__Safety Summary:__ The safety profile of istradefylline at a dose of 20 mg/day and 40 mg/day was similar to placebo, with the exception of higher incidences of dyskinesia (primarily mild to moderate in severity), fall, nausea, and insomnia.

Study drug was generally well-tolerated in all patients who were randomized.

Discussion:
In this study, istradefylline did not separate from placebo in the statistical analysis of the primary endpoint (change from baseline in hours/day spent in the OFF state). This may be related to the different patient population assessed in this study (ie, a specialized, maximally treated population that consisted of patients with PD with end-of-dose wearing-off and dyskinesia who were treated with high-dose LD (≥400 mg/day) and at least 1 other anti-parkinson medication) compared with previous studies that identified significant reduction in OFF time with istradefylline. Manuscript Table 1 shows that compared with the 7 other randomized, controlled trials (RCTs) of istradefylline, patients in Study 6002-014, had the:
- Longest mean time since starting LD of 8.7 years compared with the 7 other RCTs, which ranged from 7.2 to 8.1 years
- Longest mean time since the onset of motor complications of 6.0 years compared with the 7 other RCTs, which ranged from 3.1 to 4.5 years
- Highest baseline mean daily dose of LD of 829 mg compared with the 7 other RCTs, which ranged from 416 to 785 mg
- Matched the highest mean baseline scores for UPDRS Part III (ON) of 23 out of 108 compared with the individual studies of the 4-study pool, which ranged from 18 to 23 out of 108, despite their baseline PD treatments

Relative to the other 7 istradefylline RCTs, the patients in Study 6002-014, at baseline, also had the lowest amount of OFF time/day (5.4 hours versus a range of 5.9 to 6.7 hours, respectively), and their Modified Hoehn & Yahr scores (ON) were skewed toward the lower stages, with 72% of patients in Modified Hoehn & Yahr Stage 2 or 2.5 compared with 18% to 61% in Modified Hoehn & Yahr Stage 2 or 2.5 in the OFF state. This is consistent with patients in Study 6002-014 being maximally and optimally treated. Despite these patients taking the highest daily doses of LD (plus at least 1 additional dopaminergic agent, as required by the protocol), their baseline UPDRS Part III (ON) scores were worse than those for patients in the other istradefylline RCTs.

The baseline Modified Hoehn & Yahr Stage was recorded in the ON state in Study 6002-014 and in the OFF state for the other 7 RCTs. For patients in Study 6002-014, their best (ie, obtained in the ON state) baseline Modified Hoehn & Yahr scores were only nominally better than the worst (ie, obtained in the OFF state) baseline Modified Hoehn & Yahr scores for the other RCTs, reflecting the "maximal/optimal treatment" of patients in Study 6002-014. This suggests that for patients in Study 6002-014, PD symptoms were managed as well as possible at baseline with pharmacotherapy (LD plus at least 1 additional dopaminergic agent). Perhaps there was less room for further improvement, even after addition of another oral PD therapy in a different pharmacologic class.

Conclusions:
This study did not show a statistically significant separation from placebo for the change from baseline in the total hours/day spent in the OFF state at Week 12. This maximally treated refractory population consisted of patients with PD with motor fluctuations and dyskinesia who were treated with high-dose LD and at least one other anti-parkinson medication. Istradefylline 20 mg/day and 40 mg/day, when added as

adjunctive therapy, resulted in numerical decreases in OFF time for both istradefylline treatment groups over time that were consistently less than placebo with a safety profile that was similar to placebo. Istradefylline was well-tolerated in this study population.