SUPPORTING INFORMATION

Impact of Adjunctive Istradefylline on Dyskinesia Onset in Patients with Parkinson's Disease Exhibiting Wearing-Off: An Open-Label Randomized Controlled Trial

Yoshio Tsuboi, Takafumi Hasegawa, Yasushi Shimo, Satoshi Kaneko, Masahiko Tomiyama, Kenichi Kashihara, Shih-Wei Chiu, Takuhiro Yamaguchi, on behalf of the ODYSSEI study group

Corresponding author

Yoshio Tsuboi

E-mail: tsuboi0202@gmail.com

Members of the ODYSSEI study group

Masahiko Tomiyama (Aomori Prefectural Central Hospital); Jin-Ichi Nunomura (Aomori Prefectural Central Hospital); Tatsuya Ueno (Aomori Prefectural Central Hospital); Takafumi Hasegawa (Tohoku University Graduate School of Medicine); Sugeno Naoto (Tohoku University Graduate School of Medicine); Takashi Abe (Abe Neurology Clinic); Hiroshi Nomura (Hiroshi Nomura Neurology Clinic); Yasushi Shimo (Juntendo University Hospital); Taku Hatano (Juntendo University Hospital); Kazushi Takahashi (Saitama Medical University Hospital); Toshimasa Yamamoto (Saitama Medical University Hospital); Kazuko Hasegawa (National Hospital Organization Sagamihara National Hospital); Satoshi Kaneko (Kansai Medical University); Hidemoto Saiki (Kitano Hospital); Kenichi Komatsu (Kitano Hospital); Makio Takahashi (Osaka Red Cross Hospital); Hidefumi Ito (Wakayama Medical University Hospital); Ryosuke Takahashi (Kyoto University Graduate School of Medicine); Kenichi Kashihara (Okayama Kyokuto Hospital); Michio Kitayama (Okayama Kyokuto Hospital); Mitsutoshi Yamamoto (Takamatsu Neurology Clinic); Yoshio Tsuboi (Fukuoka University); Kazunori Itoh (Iwamizawa Neurological Medical Clinic); Tetsuya Maeda (Iwate Medical University Hospital);

Atsushi Takeda (National Hospital Organization Sendai-Nishitaga Hospital); Yuji Saitoh (National Center of Neurology and Psychiatry); Yuji Takahashi (National Center of Neurology and Psychiatry); Hiroto Eguchi (Juntendo University Nerima Hospital); Kunihiko Ikeguchi (Jichi Medical University Station Brain Clinic); Hitoshi Yamada (Yokohama Neurology Clinic); Shunya Takizawa (Tokai University Hospital); Eiichiro Nagata (Tokai University Hospital); Noriko Kawashima (Kawashima Neurology Clinic); Masahisa Katsuno (Nagoya University Hospital); Tatsuya Hattori (Honmachi Clinic); Keiko Toyooka (Osaka Toneyama Medical Center); Yoshihisa Tatsuoka (Tatsuoka Neurology Clinic); Takafumi Miyachi (Yanai Medical Center); Ritsuko Hanajima (Tottori University Hospital); Hidenori Matsuo (Nagasaki Kawatana Medical Center); Takayasu Fukudome (Nagasaki Kawatana Medical Center); Ryuichi Ohkubo (Fujimoto General Hospital); Yoshikazu Ugawa (Fukushima Medical University Hospital); Kazuaki Kanai (Fukushima Medical University Hospital); Hiroyasu Furuyama (Sapporo Yamanoue Hospital); Kazuo Kitagawa (Tokyo Women's Medical University Hospital); Ryoko Koike (Nishiniigata Chuo Hospital); Kazuyuki Noda (Juntendo University Shizuoka Hospital); Hidekazu Tomimoto (Mie University Hospital); Keita Matsuura (Mie University Hospital); Hiroaki Adachi (Hospital of The University of Occupational and Environmental Health); Kazuto Yoshida (Japanese Red Cross Asahikawa Hospital); Shigehisa Ura (Japanese Red Cross Asahikawa Hospital); Asako Yoritaka (Juntendo University Koshigaya Hospital); Takao Takeshima (Tominaga Hospital); Masaki Etoh (Higashiosaka City Medical Center); Hisae Sumi (Higashiosaka City Medical Center); Junji Yoshinaga (Yoshinaga Neurology Clinic); Nobutoshi Morimoto (Kagawa Prefectural Central Hospital); Yoshihiro Suzuki (Nihonkai General Hospital); Yoshinori Ishida (Takeda General Hospital); Ryuji Sakakibara (Sakura Medical Center, Toho University); Osamu Kano (Omori Medical Center, Toho University); Hiroshi Nagayama (Nippon Medical School Graduate School of Medicine); Katsuo Kimura (Yokohama City University Medical Center); Hideto Joki (Yokohama City University Hospital); Tsuyoshi Uchiyama (Seirei Hamamatsu General Hospital); Tomokazu Obi (Shizuoka Institute of Epilepsy and Neurological Disorders); Akihiko Ozaki

(Nakatsu Hospital); Kenji Murakata (Nakatsu Hospital); Manabu Inoue (Nakatsu Hospital); Shigeki Arawaka (Osaka Medical and Pharmaceutical University Hospital); Kazuo Toda (Toda Internal Medicine & Rehabilitation Clinic); Yoshihiko Nishida (Itsuki Hospital); Keisuke Suzuki (Dokkyo Medical University Hospital); Shih-Wei Chiu (Tohoku University Graduate School of Medicine); Takuhiro Yamaguchi (Tohoku University Graduate School of Medicine).

The study was approved by the responsible ethics committee/institutional review board at all of the participating sites listed above.

Supplementary Methods

Exclusion Criteria

Patients were excluded for any of the following reasons: treatment with istradefylline within 1 year or amantadine within 3 months before enrollment; dementia or a Mini Mental State Examination (MMSE) score of ≤ 23; brain surgery for Parkinson's disease (PD); current or planned treatment with enteral levodopa/carbidopa; moderate/severe liver damage; administration of strong CYP3A4 inhibitors within 14 days of enrollment; administration of antipsychotics within 3 months before enrollment; breastfeeding or pregnant women; and other patients deemed ineligible by the investigator.

Secondary Efficacy Endpoints

The secondary efficacy outcomes comprised the onset of troublesome dyskinesia, Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I–IV scores, modified Hoehn & Yahr (mH&Y) scale, 39-item Parkinson's Disease Questionnaire (PDQ-39), and MMSE. Troublesome dyskinesia was assessed by the physician based on information recorded in symptom diaries and MDS-UPDRS Part IV item 4.2, and defined as dyskinesia that caused trouble in daily life or was considered uncomfortable/painful, or if the MDS-UPDRS Part

IV 4.2 score was ≥ 3 or the patient complained of troublesome/painful dyskinesia. The use of concomitant anti-PD drugs was recorded at each visit; the levodopa daily dose and the levodopa-equivalent daily dose were included as secondary efficacy endpoints. All patients were asked to complete diaries in which they recorded their symptoms, as well as OFF time and dyskinesia. These diaries were reviewed by the investigator at each visit. MDS-UPDRS Part IV was completed at week 0 and each subsequent visit. MDS-UPDRS Parts I, II, and III, mH&Y, and PDQ-39 were completed at weeks 0 (screening for mH&Y), 28, 60, 92, 124, and 156. The efficacy outcomes were also determined at discontinuation if patients discontinued treatment prior to week 156.

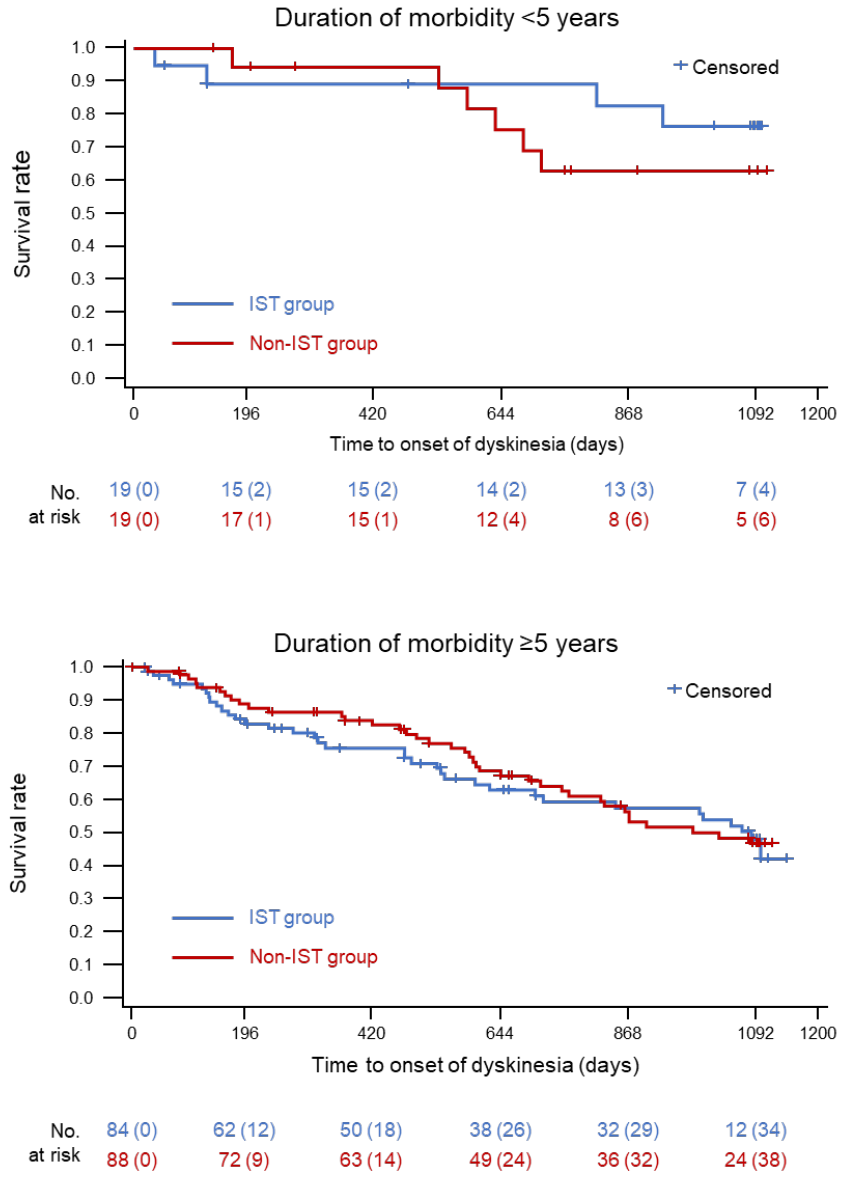
Statistical Analysis

Dyskinesia-free survival was also analyzed in patients who showed effective control of motor symptoms, defined using the following three criteria: (A) patients without an increase in the average daily OFF time over 3 days before a specified visit; or (B) patients without a worsening of the MDS-UPDRS Part III total scores in the ON phase by >4 over 3 years; or (C) patients who met criteria A and B.

Stratified analyses of the onset of dyskinesia were estimated using the stratified proportional hazard model based on the allocation factors and anticipated risk factors (age, age of PD onset, disease duration, total PDQ-39 score, total MDS-UPDRS Part III score, mH&Y severity classification, body mass index, and levodopa-equivalent daily dose [LEDD]). These factors and cutoff values for subgroups were selected conceptually, in consideration of existing knowledge or to divide patients into equal-sized subgroups based on median values. All subgroup analyses were pre-planned and specified in the statistical analysis plan.

Regarding the secondary efficacy endpoints, the Kaplan–Meier method was applied to the time to onset of troublesome dyskinesia; general linear models were used for MDS-UPDRS, PDQ-39, MMSE, daily levodopa dose, and LEDD; and the proportional odds model was used for mH&Y scale. The percentages of patients prescribed concomitant anti-PD drugs were calculated for both groups. Adverse events and adverse drug reactions were tabulated in terms of the number of events, number of patients, and percentage of patients.

Fig. S1. Kaplan–Meier analysis of time to onset of dyskinesia in patients stratified by duration of morbidity (< 5 or ≥ 5 years)

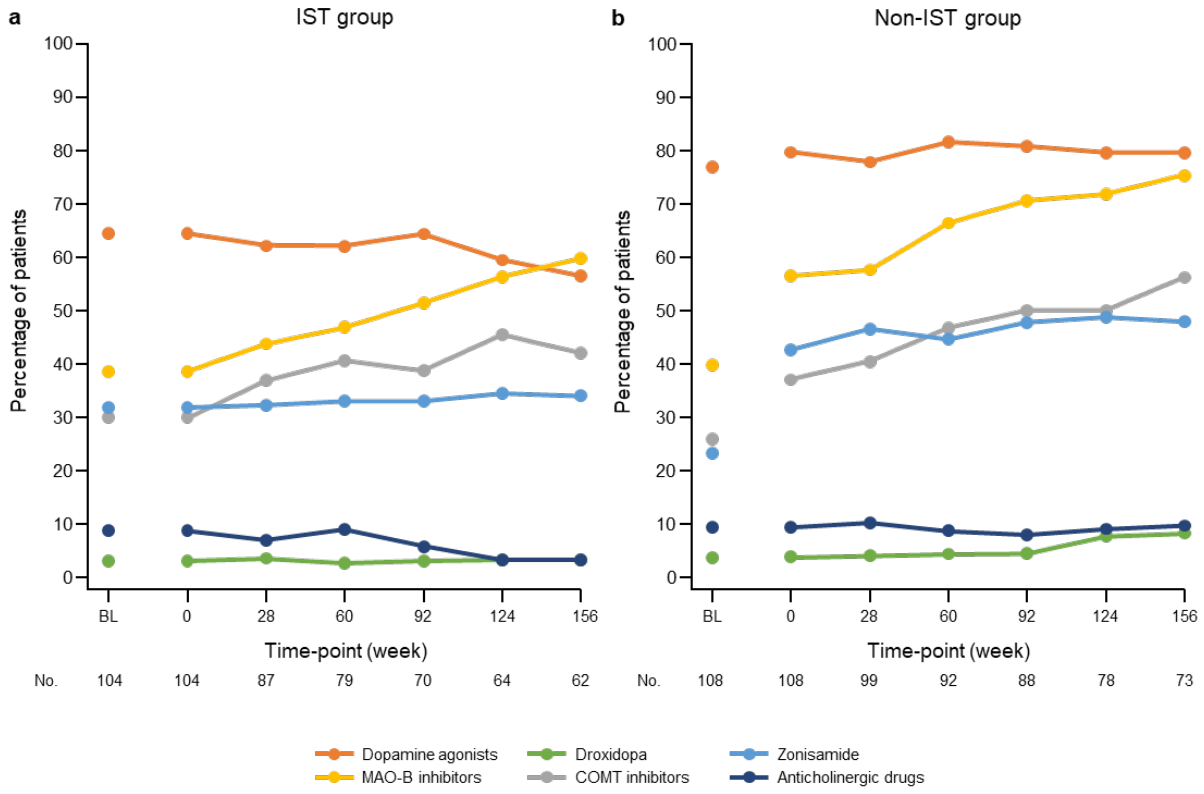


Incidence of dyskinesia (%)

Duration of morbidity	IST group	Non-IST group
<5 years	21.1	31.6
≥5 years	41.7	43.2

IST istradefylline

Fig. S2. Percentages of patients in the IST group (a) and non-IST group (b) prescribed concomitant anti-PD therapies



BL baseline, *COMT* catechol-*O*-methyl transferase, *IST* istradefylline, *MAO-B* monoamine oxidase B, *PD* Parkinson's disease