

Drug Safety

Safety and effectiveness of rasagiline in Chinese patients with Parkinson's disease: a prospective, multicenter, non-interventional post-marketing study

Running title: Rasagiline in Chinese patients with Parkinson's Disease

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Supplementary Information

Materials and Methods

Study Population

A total of 745 patients signed the ICF, of whom 6 patients were missing the date of initial rasagiline and 11 patients did not have a safety assessment completed. Therefore, the SP was comprised of 734 patients, 95 patients taking rasagiline as monotherapy and 639 as an adjunct to levodopa. In total 696 patients had at least one paired baseline and post-baseline efficacy assessment (UPDRS III, CGI-S, or CGI-I) and were therefore included in the EAS, 87 patients on monotherapy and 609 as adjunct therapy with levodopa. Data were captured at visit 2 for 695 patients, at visit 3 for 666, at visit 4 for 648 and at 696 at visit patients had at least one post-baseline visit. Week 4 data within the specified time frame (± 2 weeks) was captured from 683 patients, week 12 (± 2 weeks) from 658 patients and week 24 (± 4 weeks) from 630 patients. The mean (SD) number of days in the study since baseline was 162.4 days (44.04) with a median (Q1, Q3) of 169.0 days (155.0, 178.0) and a range of 1 to 281 days. In total, 81 patients discontinued rasagiline treatment post-baseline: 26 due to SAE/ADR, 13 due to insufficient efficacy; 3 for poor compliance; 12 were lost to follow-up; 14 withdrew consent for the study and 13 for other reasons. In total, 653 patients completed 24 weeks of the study.

Reporting AE

AEs were spontaneously reported by the patient or observed by the investigator using an AE/adverse drug reaction (ADR) report form. All serious AEs (SAEs) were required to be reported by the investigator within 24h of him/her becoming aware of them, serious ADRs (SADRs) and pregnancies/breastfeeding within three days, and non-serious ADRs within one week. Appropriately qualified personnel coded the ADRs using the lowest level term according to MedDRA version 22.0. This information was collected in a unified manner across the 20 centers. The investigator assessed the relationship of the AE to the drug, and recorded it on the AE/ADR report form. The causality was divided into 1) probable: the AE has a strong temporal relationship to the drug or recurs on rechallenge, and another etiology is unlikely or significantly less likely; 2) possible: the AE has a suggestive temporal relationship to the drug, and an alternative etiology is equally or less likely; 3) not related: the AE has no temporal relationship to the drug or is due to underlying/concurrent illness or effect of another medicinal product (that is, there is no causal relationship between the drug and the AE). An ADR is an AE that is assessed as at least possibly related to the drug. SAE/SADR was judged by the principal investigator, defined as any AE/ADR that: 1) results in death; 2) is life-threatening (this refers to an AE/ADR in which the patient was at risk of death at the time of an AE/ADR; it does not refer to an AE/ADR that hypothetically might have caused death had it been more severe); 3) requires inpatient hospitalization or prolongation of existing hospitalization; 4) results in persistent or significant disability/incapacity; 5) is a congenital anomaly/birth defect; 6) is medically important (this

refers to an AE/ADR that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent any of the SAEs/SADRs defined above).

Supplementary Table S1. Schedule of assessments

Visit	1	2	3	4
Time of visit (week)	Baseline*	4±2	12±4	24±4 or early withdrawal
Patient information / consent	X			
Physician-rated assessments				
Date of diagnosis of PD	X			
Baseline characteristics	X			
Disease history	X			
Hoehn-Yahr scale	X			
History of treatment for PD	X			
Current medication	X	X	X	X
UPDRS part III	X	X	X	X
CGI-S	X	X	X	X
CGI-I		X	X	X
SAE/ADRs	X	X	X	X

* Baseline is the day of study inclusion (the date of, or within 7 days after, first rasagiline prescription).

PD, Parkinson's disease; UPDRS, the Unified Parkinson's Disease Rating Scale; CGI-S, the Clinical Global Impression-Severity; CGI-I, the Clinical Global Impression-Global Improvement; SAE, serious adverse event; ADR, adverse drug reaction.

Supplementary Table S2. Medical history and comorbid conditions (safety population)

	Monotherapy (n=95)	Adjunct therapy (n=639)	All (n=734)
Hepatic impairment	3 (3.2%)	4 (0.6%)	7 (1.0%)
Renal impairment	3 (3.2%)	7 (1.1%)	10 (1.4%)
Patients with at least one medical history	69 (68.3%)	415 (65.3%)	484 (65.7%)
Blood and lymphatic system disorders	1 (1.0%)	7 (1.1%)	8 (1.1%)
Thrombocytosis	1 (1.0%)	1 (0.2%)	2 (0.3%)
Anaemia	0	1 (0.2%)	1 (0.1%)
Blood disorder	0	1 (0.2%)	1 (0.1%)
Leukopenia	0	1 (0.2%)	1 (0.1%)
Lymphadenitis	0	1 (0.2%)	1 (0.1%)
Lymphadenopathy	0	1 (0.2%)	1 (0.1%)
Spleen disorder	0	1 (0.2%)	1 (0.1%)
Splenic cyst	0	1 (0.2%)	1 (0.1%)
Cardiac disorders	9 (8.9%)	66 (10.4%)	75 (10.2%)
Coronary artery disease	5 (5.0%)	33 (5.2%)	38 (5.2%)
Arteriosclerosis coronary artery	1 (1.0%)	8 (1.3%)	9 (1.2%)
Atrial fibrillation	1 (1.0%)	8 (1.3%)	9 (1.2%)
Arrhythmia	2 (2.0%)	5 (0.8%)	7 (0.9%)
Coronary artery stenosis	1 (1.0%)	3 (0.5%)	4 (0.5%)
Palpitations	0	3 (0.5%)	3 (0.4%)
Supraventricular extrasystoles	1 (1.0%)	2 (0.3%)	3 (0.4%)
Hypertensive heart disease	0	2 (0.3%)	2 (0.3%)
Supraventricular tachycardia	0	2 (0.3%)	2 (0.3%)
Angina pectoris	1 (1.0%)	0	1 (0.1%)
Atrial tachycardia	0	1 (0.2%)	1 (0.1%)
Bundle branch block left	0	1 (0.2%)	1 (0.1%)
Bundle branch block right	0	1 (0.2%)	1 (0.1%)

Carditis	0	1 (0.2%)	1 (0.1%)
Congestive cardiomyopathy	0	1 (0.2%)	1 (0.1%)
Extrasystoles	0	1 (0.2%)	1 (0.1%)
Left ventricular hypertrophy	0	1 (0.2%)	1 (0.1%)
Myocardial infarction	0	1 (0.2%)	1 (0.1%)
Myocardial ischaemia	0	1 (0.2%)	1 (0.1%)
Pericardial effusion	0	1 (0.2%)	1 (0.1%)
Sinus bradycardia	0	1 (0.2%)	1 (0.1%)
Ventricular extrasystoles	0	1 (0.2%)	1 (0.1%)
Congenital, familial and genetic disorders	1 (1.0%)	7 (1.1%)	8 (1.1%)
Myocardial bridging	0	4 (0.6%)	4 (0.5%)
Atrial septal defect	0	1 (0.2%)	1 (0.1%)
Congenital heart valve disorder	0	1 (0.2%)	1 (0.1%)
Dolichocolon	1 (1.0%)	0	1 (0.1%)
Heart disease congenital	0	1 (0.2%)	1 (0.1%)
Ventricular septal defect	0	1 (0.2%)	1 (0.1%)
XXX syndrome	0	1 (0.2%)	1 (0.1%)
Ear and labyrinth disorders	0	6 (0.9%)	6 (0.8%)
Vertigo	0	2 (0.3%)	2 (0.3%)
Deafness neurosensory	0	1 (0.2%)	1 (0.1%)
Dysacusis	0	1 (0.2%)	1 (0.1%)
Meniere's disease	0	1 (0.2%)	1 (0.1%)
Vestibular disorder	0	1 (0.2%)	1 (0.1%)
Endocrine disorders	9 (8.9%)	27 (4.2%)	36 (4.9%)
Hypothyroidism	3 (3.0%)	10 (1.6%)	13 (1.8%)
Thyroid mass	1 (1.0%)	10 (1.6%)	11 (1.5%)
Hyperthyroidism	2 (2.0%)	4 (0.6%)	6 (0.8%)
Goitre	1 (1.0%)	1 (0.2%)	2 (0.3%)

Thyroid cyst	1 (1.0%)	1 (0.2%)	2 (0.3%)
Adrenal mass	0	1 (0.2%)	1 (0.1%)
Hyperparathyroidism	1 (1.0%)	0	1 (0.1%)
Eye disorders	2 (2.0%)	18 (2.8%)	20 (2.7%)
Cataract	1 (1.0%)	11 (1.7%)	12 (1.6%)
Xerophthalmia	0	5 (0.8%)	5 (0.7%)
Dry eye	1 (1.0%)	2 (0.3%)	3 (0.4%)
Blepharospasm	0	1 (0.2%)	1 (0.1%)
Glaucoma	0	1 (0.2%)	1 (0.1%)
Macular degeneration	0	1 (0.2%)	1 (0.1%)
Neovascular age-related macular degeneration	0	1 (0.2%)	1 (0.1%)
Retinal detachment	0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorders	10 (9.9%)	55 (8.6%)	65 (8.8%)
Constipation	1 (1.0%)	21 (3.3%)	22 (3.0%)
Chronic gastritis	6 (5.9%)	13 (2.0%)	19 (2.6%)
Gastroesophageal reflux disease	0	5 (0.8%)	5 (0.7%)
Duodenal ulcer	1 (1.0%)	3 (0.5%)	4 (0.5%)
Haemorrhoids	2 (2.0%)	2 (0.3%)	4 (0.5%)
Gastritis	0	3 (0.5%)	3 (0.4%)
Abdominal pain upper	0	2 (0.3%)	2 (0.3%)
Colitis	0	2 (0.3%)	2 (0.3%)
Duodenitis	0	2 (0.3%)	2 (0.3%)
Gastric ulcer	0	2 (0.3%)	2 (0.3%)
Abdominal discomfort	0	1 (0.2%)	1 (0.1%)
Duodenal ulcer haemorrhage	0	1 (0.2%)	1 (0.1%)
Functional gastrointestinal disorder	0	1 (0.2%)	1 (0.1%)
Gastric disorder	0	1 (0.2%)	1 (0.1%)

Gastritis erosive	0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorder	0	1 (0.2%)	1 (0.1%)
Gastrointestinal haemorrhage	1 (1.0%)	0	1 (0.1%)
Ileus paralytic	0	1 (0.2%)	1 (0.1%)
Inguinal hernia	0	1 (0.2%)	1 (0.1%)
Intestinal obstruction	0	1 (0.2%)	1 (0.1%)
Large intestine polyp	0	1 (0.2%)	1 (0.1%)
Oesophagitis	0	1 (0.2%)	1 (0.1%)
Oral lichen planus	0	1 (0.2%)	1 (0.1%)
Pancreatitis	0	1 (0.2%)	1 (0.1%)
Rectal polyp	0	1 (0.2%)	1 (0.1%)
Small intestinal obstruction	0	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions	0 (0.0%)	4 (0.6%)	4 (0.5%)
Asthenia	0	1 (0.2%)	1 (0.1%)
Gait disturbance	0	1 (0.2%)	1 (0.1%)
Hernia	0	1 (0.2%)	1 (0.1%)
Oedema peripheral	0	1 (0.2%)	1 (0.1%)
Hepatobiliary disorders	7 (6.9%)	22 (3.5%)	29 (3.9%)
Cholelithiasis	2 (2.0%)	9 (1.4%)	11 (1.5%)
Hepatic steatosis	3 (3.0%)	5 (0.8%)	8 (1.1%)
Gallbladder polyp	1 (1.0%)	4 (0.6%)	5 (0.7%)
Hepatic cyst	1 (1.0%)	1 (0.2%)	2 (0.3%)
Cholecystitis	0	1 (0.2%)	1 (0.1%)
Cholecystitis chronic	0	1 (0.2%)	1 (0.1%)
Hepatic cirrhosis	0	1 (0.2%)	1 (0.1%)
Hepatic failure	0	1 (0.2%)	1 (0.1%)
Hepatic lesion	0	1 (0.2%)	1 (0.1%)

Liver injury	1 (1.0%)	0	1 (0.1%)
Primary biliary cholangitis	1 (1.0%)	0	1 (0.1%)
Immune system disorders	1 (1.0%)	0	1 (0.1%)
Sarcoidosis	1 (1.0%)	0	1 (0.1%)
Infections and infestations	5 (5.0%)	32 (5.0%)	37 (5.0%)
Pharyngitis	1 (1.0%)	6 (0.9%)	7 (0.9%)
Appendicitis	1 (1.0%)	3 (0.5%)	4 (0.5%)
Hepatitis B	1 (1.0%)	3 (0.5%)	4 (0.5%)
Viral hepatitis carrier	0	4 (0.6%)	4 (0.5%)
Conjunctivitis	1 (1.0%)	2 (0.3%)	3 (0.4%)
Tuberculosis	0	3 (0.5%)	3 (0.4%)
Rhinitis	0	2 (0.3%)	2 (0.3%)
Arthritis infective	0	1 (0.2%)	1 (0.1%)
Bacterial vulvovaginitis	0	1 (0.2%)	1 (0.1%)
Bronchitis	0	1 (0.2%)	1 (0.1%)
Chronic hepatitis B	0	1 (0.2%)	1 (0.1%)
Encephalitis	0	1 (0.2%)	1 (0.1%)
Gastroenteritis	0	1 (0.2%)	1 (0.1%)
Helicobacter infection	1 (1.0%)	0	1 (0.1%)
Hepatitis A	0	1 (0.2%)	1 (0.1%)
Hepatitis C	0	1 (0.2%)	1 (0.1%)
Hepatitis E	0	1 (0.2%)	1 (0.1%)
Liver abscess	0	1 (0.2%)	1 (0.1%)
Lymph node tuberculosis	0	1 (0.2%)	1 (0.1%)
Meningitis viral	0	1 (0.2%)	1 (0.1%)
Otitis externa	0	1 (0.2%)	1 (0.1%)
Otosalpingitis	0	1 (0.2%)	1 (0.1%)
Periodontitis	0	1 (0.2%)	1 (0.1%)

Pulmonary tuberculosis	0	1 (0.2%)	1 (0.1%)
Schistosomiasis liver	0	1 (0.2%)	1 (0.1%)
Sinusitis	0	1 (0.2%)	1 (0.1%)
Tracheitis	0	1 (0.2%)	1 (0.1%)
Injury, poisoning and procedural complications	4 (4.0%)	14 (2.2%)	18 (2.4%)
Lumbar vertebral fracture	0	3 (0.5%)	3 (0.4%)
Upper limb fracture	2 (2.0%)	1 (0.2%)	3 (0.4%)
Head injury	0	2 (0.3%)	2 (0.3%)
Joint injury	1 (1.0%)	1 (0.2%)	2 (0.3%)
Muscle strain	1 (1.0%)	1 (0.2%)	2 (0.3%)
Rib fracture	1 (1.0%)	1 (0.2%)	2 (0.3%)
Craniocerebral injury	0	1 (0.2%)	1 (0.1%)
Fracture	0	1 (0.2%)	1 (0.1%)
Fractured coccyx	0	1 (0.2%)	1 (0.1%)
Ligament sprain	0	1 (0.2%)	1 (0.1%)
Spinal compression fracture	1 (1.0%)	0	1 (0.1%)
Spinal fracture	0	1 (0.2%)	1 (0.1%)
Investigations	1 (1.0%)	9 (1.4%)	10 (1.4%)
Bone density decreased	0	3 (0.5%)	3 (0.4%)
Blood glucose increased	0	1 (0.2%)	1 (0.1%)
Carcinoembryonic antigen increased	0	1 (0.2%)	1 (0.1%)
Diagnostic procedure	0	1 (0.2%)	1 (0.1%)
Human papilloma virus test positive	0	1 (0.2%)	1 (0.1%)
Lipids increased	1 (1.0%)	0	1 (0.1%)
Prostatic specific antigen increased	0	1 (0.2%)	1 (0.1%)
Ureteroscopy	0	1 (0.2%)	1 (0.1%)
Metabolism and nutrition disorders	24 (23.8%)	106 (16.7%)	130 (17.6%)

Diabetes mellitus	8 (7.9%)	41 (6.4%)	49 (6.6%)
Hyperlipidaemia	8 (7.9%)	39 (6.1%)	47 (6.4%)
Type 2 diabetes mellitus	4 (4.0%)	16 (2.5%)	20 (2.7%)
Hyperuricaemia	3 (3.0%)	6 (0.9%)	9 (1.2%)
Gout	1 (1.0%)	6 (0.9%)	7 (0.9%)
Hyperhomocysteinaemia	0	7 (1.1%)	7 (0.9%)
Dyslipidaemia	1 (1.0%)	1 (0.2%)	2 (0.3%)
Hypercholesterolaemia	1 (1.0%)	1 (0.2%)	2 (0.3%)
Hyperglycaemia	0	2 (0.3%)	2 (0.3%)
Folate deficiency	0	1 (0.2%)	1 (0.1%)
Glucose tolerance impaired	0	1 (0.2%)	1 (0.1%)
Overweight	0	1 (0.2%)	1 (0.1%)
Vitamin D deficiency	0	1 (0.2%)	1 (0.1%)
Musculoskeletal and connective tissue disorders	13 (12.9%)	95 (14.9%)	108 (14.7%)
Intervertebral disc protrusion	2 (2.0%)	31 (4.9%)	33 (4.5%)
Osteoporosis	6 (5.9%)	19 (3.0%)	25 (3.4%)
Spinal osteoarthritis	2 (2.0%)	19 (3.0%)	21 (2.8%)
Osteoarthritis	2 (2.0%)	11 (1.7%)	13 (1.8%)
Arthralgia	2 (2.0%)	9 (1.4%)	11 (1.5%)
Arthritis	2 (2.0%)	4 (0.6%)	6 (0.8%)
Rheumatoid arthritis	0	4 (0.6%)	4 (0.5%)
Back pain	1 (1.0%)	2 (0.3%)	3 (0.4%)
Lumbar spinal stenosis	0	3 (0.5%)	3 (0.4%)
Osteoarthropathy	1 (1.0%)	2 (0.3%)	3 (0.4%)
Periarthritis	0	3 (0.5%)	3 (0.4%)
Spondylolisthesis	0	3 (0.5%)	3 (0.4%)
Arthropathy	0	2 (0.3%)	2 (0.3%)

Cervical spinal stenosis	0	2 (0.3%)	2 (0.3%)
Intervertebral disc disorder	0	2 (0.3%)	2 (0.3%)
Sjogren's syndrome	0	2 (0.3%)	2 (0.3%)
Bone formation increased	0	1 (0.2%)	1 (0.1%)
Exostosis	0	1 (0.2%)	1 (0.1%)
Finger deformity	0	1 (0.2%)	1 (0.1%)
Haemarthrosis	0	1 (0.2%)	1 (0.1%)
Joint effusion	0	1 (0.2%)	1 (0.1%)
Muscular weakness	1 (1.0%)	0	1 (0.1%)
Musculoskeletal pain	0	1 (0.2%)	1 (0.1%)
Osteonecrosis	0	1 (0.2%)	1 (0.1%)
Sarcopenia	0	1 (0.2%)	1 (0.1%)
Scoliosis	0	1 (0.2%)	1 (0.1%)
Spinal stenosis	0	1 (0.2%)	1 (0.1%)
Synovitis	0	1 (0.2%)	1 (0.1%)
Tenosynovitis	0	1 (0.2%)	1 (0.1%)
Torticollis	0	1 (0.2%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (3.0%)	35 (5.5%)	38 (5.2%)
Uterine leiomyoma	0	8 (1.3%)	8 (1.1%)
Breast cancer	1 (1.0%)	5 (0.8%)	6 (0.8%)
Lung neoplasm malignant	0	4 (0.6%)	4 (0.5%)
Thyroid cancer	1 (1.0%)	2 (0.3%)	3 (0.4%)
Endometrial cancer	1 (1.0%)	1 (0.2%)	2 (0.3%)
Basal cell carcinoma	0	1 (0.2%)	1 (0.1%)
Bladder neoplasm	0	1 (0.2%)	1 (0.1%)
Cerebral haemangioma	0	1 (0.2%)	1 (0.1%)
Colon adenoma	0	1 (0.2%)	1 (0.1%)

Fibroadenoma of breast	0	1 (0.2%)	1 (0.1%)
Gallbladder cancer	0	1 (0.2%)	1 (0.1%)
Gastric cancer	0	1 (0.2%)	1 (0.1%)
Gastrointestinal stromal tumour	0	1 (0.2%)	1 (0.1%)
Gastrointestinal tract adenoma	0	1 (0.2%)	1 (0.1%)
Haemangioma	0	1 (0.2%)	1 (0.1%)
Haemangioma of liver	0	1 (0.2%)	1 (0.1%)
Lipoma	1 (1.0%)	0	1 (0.1%)
Lymphoma	0	1 (0.2%)	1 (0.1%)
Nasopharyngeal cancer	0	1 (0.2%)	1 (0.1%)
Prostate cancer	0	1 (0.2%)	1 (0.1%)
Renal cell carcinoma	0	1 (0.2%)	1 (0.1%)
Thyroid neoplasm	0	1 (0.2%)	1 (0.1%)
Vascular neoplasm	0	1 (0.2%)	1 (0.1%)
Nervous system disorders	10 (9.9%)	103 (16.2%)	113 (15.3%)
Lacunar infarction	3 (3.0%)	29 (4.6%)	32 (4.3%)
Cerebral infarction	3 (3.0%)	26 (4.1%)	29 (3.9%)
Carotid arteriosclerosis	0	14 (2.2%)	14 (1.9%)
Cerebral ischaemia	1 (1.0%)	11 (1.7%)	12 (1.6%)
Cerebrovascular disorder	0	7 (1.1%)	7 (0.9%)
Cerebral atrophy	0	6 (0.9%)	6 (0.8%)
Dizziness	1 (1.0%)	5 (0.8%)	6 (0.8%)
Facial paralysis	0	5 (0.8%)	5 (0.7%)
Cerebral arteriosclerosis	0	4 (0.6%)	4 (0.5%)
Neuropathy peripheral	1 (1.0%)	3 (0.5%)	4 (0.5%)
Cognitive disorder	0	3 (0.5%)	3 (0.4%)
Ischaemic cerebral infarction	0	3 (0.5%)	3 (0.4%)
Carotid artery disease	0	2 (0.3%)	2 (0.3%)

Essential tremor	1 (1.0%)	1 (0.2%)	2 (0.3%)
Headache	0	2 (0.3%)	2 (0.3%)
Restless legs syndrome	0	2 (0.3%)	2 (0.3%)
Tremor	1 (1.0%)	1 (0.2%)	2 (0.3%)
Balance disorder	0	1 (0.2%)	1 (0.1%)
Carpal tunnel syndrome	0	1 (0.2%)	1 (0.1%)
Cerebral artery occlusion	0	1 (0.2%)	1 (0.1%)
Cerebral haemorrhage	1 (1.0%)	0	1 (0.1%)
Cerebroscclerosis	0	1 (0.2%)	1 (0.1%)
Cerebrovascular insufficiency	0	1 (0.2%)	1 (0.1%)
Dementia	0	1 (0.2%)	1 (0.1%)
Diabetic neuropathy	0	1 (0.2%)	1 (0.1%)
Epilepsy	0	1 (0.2%)	1 (0.1%)
Hypoaesthesia	0	1 (0.2%)	1 (0.1%)
Intracranial aneurysm	1 (1.0%)	0	1 (0.1%)
Lumbar radiculopathy	0	1 (0.2%)	1 (0.1%)
Memory impairment	0	1 (0.2%)	1 (0.1%)
Peripheral paralysis	0	1 (0.2%)	1 (0.1%)
Pineal gland cyst	0	1 (0.2%)	1 (0.1%)
Sciatica	0	1 (0.2%)	1 (0.1%)
Transient ischaemic attack	0	1 (0.2%)	1 (0.1%)
Vertebral artery stenosis	0	1 (0.2%)	1 (0.1%)
Pregnancy, puerperium and perinatal conditions	0	1 (0.2%)	1 (0.1%)
Ectopic pregnancy	0	1 (0.2%)	1 (0.1%)
Product issues	0	1 (0.2%)	1 (0.1%)
Device physical property issue	0	1 (0.2%)	1 (0.1%)
Psychiatric disorders	3 (3.0%)	29 (4.6%)	32 (4.3%)

Depression	1 (1.0%)	13 (2.0%)	14 (1.9%)
Sleep disorder	1 (1.0%)	9 (1.4%)	10 (1.4%)
Anxiety	1 (1.0%)	4 (0.6%)	5 (0.7%)
Anxiety disorder	0	3 (0.5%)	3 (0.4%)
Insomnia	0	2 (0.3%)	2 (0.3%)
Hallucination	0	1 (0.2%)	1 (0.1%)
Impulse-control disorder	0	1 (0.2%)	1 (0.1%)
Major depression	0	1 (0.2%)	1 (0.1%)
Mental disorder	0	1 (0.2%)	1 (0.1%)
Rapid eye movement sleep behaviour disorder	0	1 (0.2%)	1 (0.1%)
Renal and urinary disorders	5 (5.0%)	20 (3.1%)	25 (3.4%)
Renal cyst	2 (2.0%)	8 (1.3%)	10 (1.4%)
Nephrolithiasis	0	6 (0.9%)	6 (0.8%)
Calculus urinary	1 (1.0%)	1 (0.2%)	2 (0.3%)
Dysuria	1 (1.0%)	0	1 (0.1%)
Glomerulonephritis chronic	1 (1.0%)	0	1 (0.1%)
Glycosuria	1 (1.0%)	0	1 (0.1%)
Hydronephrosis	0	1 (0.2%)	1 (0.1%)
Nephritis	1 (1.0%)	0	1 (0.1%)
Neurogenic bladder	0	1 (0.2%)	1 (0.1%)
Renal failure	0	1 (0.2%)	1 (0.1%)
Renal impairment	0	1 (0.2%)	1 (0.1%)
Ureteric stenosis	0	1 (0.2%)	1 (0.1%)
Urinary incontinence	0	1 (0.2%)	1 (0.1%)
Reproductive system and breast disorders	7 (6.9%)	37 (5.8%)	44 (6.0%)
Benign prostatic hyperplasia	3 (3.0%)	29 (4.6%)	32 (4.3%)
Prostatitis	0	3 (0.5%)	3 (0.4%)

Breast hyperplasia	1 (1.0%)	1 (0.2%)	2 (0.3%)
Balanoposthitis	0	1 (0.2%)	1 (0.1%)
Breast mass	1 (1.0%)	0	1 (0.1%)
Cervical discharge	1 (1.0%)	0	1 (0.1%)
Cervical dysplasia	0	1 (0.2%)	1 (0.1%)
Menopausal symptoms	1 (1.0%)	0	1 (0.1%)
Ovarian cyst	1 (1.0%)	0	1 (0.1%)
Perineal pain	0	1 (0.2%)	1 (0.1%)
Prostatic cyst	0	1 (0.2%)	1 (0.1%)
Uterine prolapse	1 (1.0%)	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	3 (3.0%)	23 (3.6%)	26 (3.5%)
Pulmonary mass	0	6 (0.9%)	6 (0.8%)
Asthma	1 (1.0%)	3 (0.5%)	4 (0.5%)
Chronic obstructive pulmonary disease	0	4 (0.6%)	4 (0.5%)
Bronchiectasis	1 (1.0%)	2 (0.3%)	3 (0.4%)
Bronchitis chronic	1 (1.0%)	2 (0.3%)	3 (0.4%)
Emphysema	0	2 (0.3%)	2 (0.3%)
Pulmonary embolism	0	2 (0.3%)	2 (0.3%)
Rhinitis allergic	0	2 (0.3%)	2 (0.3%)
Sleep apnoea syndrome	0	2 (0.3%)	2 (0.3%)
Cough variant asthma	0	1 (0.2%)	1 (0.1%)
Cystic lung disease	0	1 (0.2%)	1 (0.1%)
Obstructive airways disorder	0	1 (0.2%)	1 (0.1%)
Paranasal cyst	0	1 (0.2%)	1 (0.1%)
Productive cough	0	1 (0.2%)	1 (0.1%)
Pulmonary fibrosis	0	1 (0.2%)	1 (0.1%)
Skin and subcutaneous tissue disorders	4 (4.0%)	8 (1.3%)	12 (1.6%)

Eczema	1 (1.0%)	4 (0.6%)	5 (0.7%)
Dermatitis allergic	0	1 (0.2%)	1 (0.1%)
Livedo reticularis	0	1 (0.2%)	1 (0.1%)
Psoriasis	1 (1.0%)	0	1 (0.1%)
Seborrhoeic dermatitis	0	1 (0.2%)	1 (0.1%)
Skin mass	1 (1.0%)	0	1 (0.1%)
Urticaria	0	1 (0.2%)	1 (0.1%)
Vitiligo	1 (1.0%)	0	1 (0.1%)
Surgical and medical procedures	2 (2.0%)	78 (12.3%)	80 (10.9%)
Cholecystectomy	1 (1.0%)	11 (1.7%)	12 (1.6%)
Deep brain stimulation	0	11 (1.7%)	11 (1.5%)
Appendicectomy	0	8 (1.3%)	8 (1.1%)
Coronary arterial stent insertion	0	7 (1.1%)	7 (0.9%)
Spinal operation	0	5 (0.8%)	5 (0.7%)
Cancer surgery	0	4 (0.6%)	4 (0.5%)
Cataract operation	0	3 (0.5%)	3 (0.4%)
Fracture treatment	0	3 (0.5%)	3 (0.4%)
Hysterectomy	0	3 (0.5%)	3 (0.4%)
Nephrectomy	0	3 (0.5%)	3 (0.4%)
Thyroidectomy	0	3 (0.5%)	3 (0.4%)
Cholelithotomy	0	2 (0.3%)	2 (0.3%)
Haemorrhoid operation	0	2 (0.3%)	2 (0.3%)
Intervertebral disc operation	0	2 (0.3%)	2 (0.3%)
Knee arthroplasty	0	2 (0.3%)	2 (0.3%)
Myomectomy	0	2 (0.3%)	2 (0.3%)
Thyroid cystectomy	0	2 (0.3%)	2 (0.3%)
Tumor excision	0	2 (0.3%)	2 (0.3%)
Aortic aneurysm repair	0	1 (0.2%)	1 (0.1%)

Benign breast lump removal	0	1 (0.2%)	1 (0.1%)
Benign tumour excision	0	1 (0.2%)	1 (0.1%)
Biliary tract operation	0	1 (0.2%)	1 (0.1%)
Brain operation	0	1 (0.2%)	1 (0.1%)
Brain tumor operation	0	1 (0.2%)	1 (0.1%)
Cardiac ablation	0	1 (0.2%)	1 (0.1%)
Cardiac pacemaker insertion	0	1 (0.2%)	1 (0.1%)
Carotid artery stent insertion	0	1 (0.2%)	1 (0.1%)
Cerebral endovascular aneurysm repair	1 (1.0%)	0	1 (0.1%)
Cranial nerve decompression	0	1 (0.2%)	1 (0.1%)
Electrocorticogram electrodes placement	0	1 (0.2%)	1 (0.1%)
Finger repair operation	0	1 (0.2%)	1 (0.1%)
Haemangioma removal	0	1 (0.2%)	1 (0.1%)
Inguinal hernia repair	0	1 (0.2%)	1 (0.1%)
Mastectomy	0	1 (0.2%)	1 (0.1%)
Meniscus operation	0	1 (0.2%)	1 (0.1%)
Nasal polypectomy	0	1 (0.2%)	1 (0.1%)
Neuroprosthesis implantation	0	1 (0.2%)	1 (0.1%)
Ovarian cystectomy	0	1 (0.2%)	1 (0.1%)
Pallidotomy	0	1 (0.2%)	1 (0.1%)
Prostatic operation	0	1 (0.2%)	1 (0.1%)
Rectal polypectomy	0	1 (0.2%)	1 (0.1%)
Salpingectomy	0	1 (0.2%)	1 (0.1%)
Shoulder operation	0	1 (0.2%)	1 (0.1%)
Stent placement	0	1 (0.2%)	1 (0.1%)
Venous operation	0	1 (0.2%)	1 (0.1%)
Vascular disorders	39 (38.6%)	180 (28.3%)	219 (29.7%)
Hypertension	37 (36.6%)	162 (25.5%)	199 (27.0%)

Arteriosclerosis	2 (2.0%)	14 (2.2%)	16 (2.2%)
Varicose vein	2 (2.0%)	2 (0.3%)	4 (0.5%)
Aortic arteriosclerosis	0	3 (0.5%)	3 (0.4%)
Peripheral arterial occlusive disease	0	3 (0.5%)	3 (0.4%)
Arterial stenosis	0	2 (0.3%)	2 (0.3%)
Orthostatic hypotension	0	2 (0.3%)	2 (0.3%)
Deep vein thrombosis	0	1 (0.2%)	1 (0.1%)
Diabetic vascular disorder	0	1 (0.2%)	1 (0.1%)
Essential hypertension	0	1 (0.2%)	1 (0.1%)
Hypotension	0	1 (0.2%)	1 (0.1%)
Venous thrombosis limb	0	1 (0.2%)	1 (0.1%)

Supplementary Table S3. Prior and concomitant medications (safety population)

	Monotherapy (n=95)	Adjunct therapy (n=639)	All (n=734)
Prior anti-PD medications	29 (30.5%)	168 (26.3%)	197 (26.8%)
MAO-BIs			
Rasagiline	0 (0.0%)	4 (0.6%)	4 (0.5%)
Selegiline	5 (5.3%)	76 (11.9%)	81 (11.0%)
Compound levodopa			
Carbidopa, entacapone, levodopa	0 (0.0%)	3 (0.5%)	3 (0.4%)
Carbidopa, levodopa	0 (0.0%)	11 (1.7%)	11 (1.5%)
Benserazide, levodopa	20 (21.1%)	54 (8.5%)	74 (10.1%)
DAs			
Ropinirole	0 (0.0%)	1 (0.2%)	1 (0.1%)
Rotigotine	0 (0.0%)	1 (0.2%)	1 (0.1%)
Piribedil	3 (3.2%)	11 (1.7%)	14 (1.9%)
Pramipexole	7 (7.4%)	41 (6.4%)	48 (6.5%)
COMTIs			
Entacapone	0 (0.0%)	15 (2.3%)	15 (2.0%)
Others			
Trihexyphenidyl	3 (3.2%)	5 (0.8%)	8 (1.1%)
Amantadine	3 (3.2%)	13 (2.0%)	16 (2.2%)
Prior medications other than anti-PD medications	17 (17.9%)	60 (9.4%)	77 (10.5%)
Nervous system	5 (5.3%)	29 (4.5%)	34 (4.6%)
Alimentary tract and metabolism	6 (6.3%)	21 (3.3%)	27 (3.7%)
Cardiovascular system	6 (6.3%)	18 (2.8%)	24 (3.3%)
Blood and blood forming organs	3 (3.2%)	8 (1.3%)	11 (1.5%)
Musculo-skeletal system	0 (0.0%)	9 (1.4%)	9 (1.2%)
Anti-infectives for systemic use	0 (0.0%)	7 (1.1%)	7 (1.0%)
Respiratory System	0 (0.0%)	6 (0.9%)	6 (0.8%)
Genitourinary system and sex hormones	0 (0.0%)	2 (0.3%)	2 (0.3%)
Sensory Organs	1 (1.1%)	1 (0.2%)	2 (0.3%)
Dermatological drugs	0 (0.0%)	1 (0.2%)	1 (0.1%)
Others ¹	3 (3.2%)	12 (1.9%)	15 (2.0%)
Concomitant anti-PD medications ongoing at or ended after initiation of rasagiline	95 (100.0%)	639 (100.0%)	734 (100.0%)
MAO-BIs			
Selegiline	2 (2.1%)	11 (1.7%)	13 (1.8%)
Rasagiline	95 (100.0%)	639 (100.0%)	734 (100.0%)
Levodopa/compound levodopa			
Levodopa	0 (0.0%)	1 (0.2%)	1 (0.1%)
Carbidopa, entacapone, levodopa	0 (0.0%)	11 (1.7%)	11 (1.5%)
Carbidopa, levodopa	3 (3.2%)	171 (26.8%)	174 (23.7%)
Benserazide, levodopa	10 (10.5%)	623 (97.5%)	633 (86.2%)
DAs			

Bromocriptine	0 (0.0%)	2 (0.3%)	2 (0.3%)
Rotigotine	1 (1.1%)	15 (2.3%)	16 (2.2%)
Ropinirole	1 (1.1%)	20 (3.1%)	21 (2.9%)
Piribedil	4 (4.2%)	104 (16.3%)	108 (14.7%)
Pramipexole	7 (7.4%)	402 (62.9%)	409 (55.7%)
COMTIs			
Entacapone	0 (0.0%)	170 (26.6%)	170 (23.2%)
Others			
Droxidopa	0 (0.0%)	1 (0.2%)	1 (0.1%)
Trihexyphenidyl	3 (3.2%)	50 (7.8%)	53 (7.2%)
Amantadine	3 (3.2%)	182 (28.5%)	185 (25.2%)
Concomitant anti-PD medications taken through the initiation of rasagiline	0 (0.0%)	623 (97.5%)	623 (84.9%)
MAO-BIs			
Selegiline	0 (0.0%)	2 (0.3%)	2 (0.3%)
Compound levodopa			
Carbidopa, entacapone, levodopa	0 (0.0%)	6 (0.9%)	6 (0.8%)
Carbidopa, levodopa	0 (0.0%)	130 (20.3%)	130 (17.7%)
Benserazide, levodopa	0 (0.0%)	581 (90.9%)	581 (79.2%)
DAs			
Rotigotine	0 (0.0%)	7 (1.1%)	7 (1.0%)
Ropinirole	0 (0.0%)	18 (2.8%)	18 (2.5%)
Piribedil	0 (0.0%)	93 (14.6%)	93 (12.7%)
Pramipexole	0 (0.0%)	368 (57.6%)	368 (50.1%)
COMTIs			
Entacapone	0 (0.0%)	147 (23.0%)	147 (20.0%)
Others			
Trihexyphenidyl	0 (0.0%)	39 (6.1%)	39 (5.3%)
Amantadine	0 (0.0%)	163 (25.5%)	163 (22.2%)
Concomitant medications other than anti-PD medications	69 (72.6%)	433 (67.8%)	502 (68.4%)
Alimentary tract and metabolism	30 (31.6%)	206 (32.2%)	236 (32.2%)
Anti-infectives for systemic use	4 (4.2%)	34 (5.3%)	38 (5.2%)
Antineoplastic and immunomodulating agents	0 (0.0%)	7 (1.1%)	7 (1.0%)
Blood and blood forming organs	23 (24.2%)	118 (18.5%)	141 (19.2%)
Cardiovascular system	47 (49.5%)	213 (33.3%)	260 (35.4%)
Dermatological drugs	4 (4.2%)	14 (2.2%)	18 (2.5%)
Genitourinary system and sex hormones	3 (3.2%)	29 (4.5%)	32 (4.4%)
Musculo-skeletal system	11 (11.6%)	63 (9.9%)	74 (10.1%)
Nervous system	21 (22.1%)	197 (30.8%)	218 (29.7%)
Respiratory system	5 (5.3%)	34 (5.3%)	39 (5.3%)
Sensory organs	3 (3.2%)	17 (2.7%)	20 (2.7%)
Systemic hormonal preparations, excl. sex hormones and insulins	8 (8.4%)	22 (3.4%)	30 (4.1%)
Others ²			

¹ Others included unspecified herbal and traditional medicine, antidotes, etc.

² Others included unspecified herbal and traditional medicine, amino acids, antidotes, anti-inflammatory agents, fat/carbohydrates/proteins/minerals/vitamins, general nutrients, etc.

PD, Parkinson's disease; MAO-BIs, monoamine oxidase B inhibitors; DAs, dopamine agonists; COMTIs, catechol-O-methyl transferase inhibitors.

Supplementary Table S4. Adverse drug reactions (ADRs) leading to permanent discontinuation of rasagiline (safety population)

	Monotherapy (n=95)	Adjunct therapy (n=639)	All (n=734)
Patients with at least one ADR leading to rasagiline discontinuation	4 (4.2%)	47 (7.4%)	51 (6.9%)
Cardiac disorders	0	1 (0.2%)	1 (0.1%)
Palpitations	0	1 (0.2%)	1 (0.1%)
Eye disorders	0	4 (0.6%)	4 (0.5%)
Amaurosis	0	2 (0.3%)	2 (0.3%)
Ocular hyperaemia	0	1 (0.2%)	1 (0.1%)
Vision blurred	0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorders	0	11 (1.7%)	11 (1.5%)
Nausea	0	3 (0.5%)	3 (0.4%)
Vomiting	0	3 (0.5%)	3 (0.4%)
Dry mouth	0	2 (0.3%)	2 (0.3%)
Abdominal discomfort	0	1 (0.2%)	1 (0.1%)
Constipation	0	1 (0.2%)	1 (0.1%)
Diarrhea	0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorder	0	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions	0	7 (1.1%)	7 (0.9%)
Chest discomfort	0	3 (0.5%)	3 (0.4%)
Fatigue	0	2 (0.3%)	2 (0.3%)
Malaise	0	2 (0.3%)	2 (0.3%)
Death	0	1 (0.2%)	1 (0.1%)
Immune system disorders	1 (1.0%)	0	1 (0.1%)
Hypersensitivity	1 (1.0%)	0	1 (0.1%)
Injury, poisoning and procedural complications	0	1 (0.2%)	1 (0.1%)
Fall	0	1 (0.2%)	1 (0.1%)

Investigations	1 (1.0%)	2 (0.3%)	3 (0.4%)
Blood pressure decreased	0	1 (0.2%)	1 (0.1%)
Neutrophil count decreased	1 (1.0%)	0	1 (0.1%)
Weight decreased	0	1 (0.2%)	1 (0.1%)
White blood cell count decreased	1 (1.0%)	0	1 (0.1%)
Metabolism and nutrition disorders	0	5 (0.8%)	5 (0.7%)
Decreased appetite	0	5 (0.8%)	5 (0.7%)
Musculoskeletal and connective tissue disorders	0	3 (0.5%)	3 (0.4%)
Muscular weakness	0	1 (0.2%)	1 (0.1%)
Musculoskeletal stiffness	0	1 (0.2%)	1 (0.1%)
Pain in extremity	0	1 (0.2%)	1 (0.1%)
Nervous system disorders	2 (2.0%)	20 (3.1%)	22 (3.0%)
Dizziness	2 (2.0%)	9 (1.4%)	11 (1.5%)
Dyskinesia	0	3 (0.5%)	3 (0.4%)
Headache	0	2 (0.3%)	2 (0.3%)
Autonomic nervous system imbalance	0	1 (0.2%)	1 (0.1%)
Dizziness postural	0	1 (0.2%)	1 (0.1%)
Head discomfort	1 (1.0%)	0	1 (0.1%)
Neuralgia	0	1 (0.2%)	1 (0.1%)
Paraesthesia	0	1 (0.2%)	1 (0.1%)
Parkinson's disease	0	1 (0.2%)	1 (0.1%)
Somnolence	0	1 (0.2%)	1 (0.1%)
Syncope	0	1 (0.2%)	1 (0.1%)
Psychiatric disorders	0	10 (1.6%)	10 (1.4%)
Hallucination	0	5 (0.8%)	5 (0.7%)
Hallucination, visual	0	2 (0.3%)	2 (0.3%)
Impulse-control disorder	0	1 (0.2%)	1 (0.1%)
Insomnia	0	1 (0.2%)	1 (0.1%)

Sleep disorder	0	1 (0.2%)	1 (0.1%)
Vascular disorders	0	4 (0.6%)	4 (0.5%)
Hypotension	0	2 (0.3%)	2 (0.3%)
Blood pressure fluctuation	0	1 (0.2%)	1 (0.1%)
Hypertension	0	1 (0.2%)	1 (0.1%)