SYNOPSIS

Title of the study:	A Phase II, Randomized, Multicenter, Multinational, Double-Blind, Placebo-Controlled, Study of the Effect of SR57667B on Dopaminergic Nigro-striatal Function Assessed by 18F-Dopa PET Imaging in Outpatients with Early Parkinson's Disease
Investigator:	[redacted]
Study centers:	30 active study centers in 7 countries: Canada, Finland, France, the Netherlands, Spain, Switzerland, and the United Kingdom.
Publications (reference):	None
Study period:	
Date first patient enrolled:	19 January 2004
Date last patient completed:	05 March 2007
Phase of development:	Phase 2

Objectives:

The primary objective was to study the effect of SR57667B at the dose of 4 mg/day on progression of dopaminergic nigro-striatal lesions assessed by 18-fluorodopa positron emission tomography (^{18}F-Dopa PET) imaging.

Secondary objectives were to:

- Assess the effect of SR57667B on symptomatic decline in patients with early Parkinson's disease;
- Assess the safety/tolerability of SR57667B in patients with early Parkinson's disease;
- Document plasma concentrations of SR57667 in patients with early Parkinson's disease.

Methodology: Multinational, multicenter, randomized, parallel-group, double-blind, placebo-controlled study. Randomization was stratified on the dopaminergic treatment, in 2 strata: treatment by levodopa or dopamine agonist.

Number of patients:	Planned: 160	Randomized: 183	Treated: 183
Evaluated:	Efficacy: 152	Safety: 183	Pharmacokinetics: 152

Diagnosis and criteria for inclusion: Male and female outpatients, aged ≥35 years, diagnosed with Parkinson's disease of less than 3 years duration with at least 2 of the 3 key Parkinson symptoms (ie, resting tremor, bradykinesia, and rigidity), modified Hoehn and Yahr (H&Y) stage ≤2.5, treated by levodopa or a dopamine agonist for a maximum of 2 years, with treatment stable over the 2 months preceding randomization and expected to remain stable for at least 2 months following randomization

Investigational product: Size 3 capsules containing 2 mg SR57667B

Dose: 4 mg/day

Administration: Oral route once daily in fed conditions (with breakfast)

Batch numbers: [redacted]

Duration of treatment: Planned: 24 months; mean standard deviation (SD) respectively 21.8 (6.3) and 20.8 (7.2) months in the placebo and SR57667B groups.

Duration of observation: Planned: 27.5 months (including screening, treatment, and follow-up periods)

Reference therapy: Matching size 3 placebo capsules

Dose: 0

Administration: Oral route once daily in fed conditions (with breakfast)

Batch numbers: [redacted]

Criteria for evaluation:

Efficacy:

Primary variable***:*** ^{18}F-Dopa PET scans at baseline and end of treatment

Secondary variable***:***

- Unified Parkinson's Disease Rating Scale (UPDRS) total score and subscores

Safety: Monitoring of adverse events, clinical laboratory evaluations (hematology, blood chemistry, urinalysis), vital signs, electrocardiogram (ECG) parameters, and physical examinations.

Pharmacokinetics: Plasma concentrations of SR57667.

Pharmacokinetic sampling times and bioanalytical method: Blood samples for quantification of SR57667 concentrations in plasma were collected on Day 14, and at Months 1, 2, 4, 6, 9, 12, 18, 24, and 27 after repeated oral administration of SR57667B 4 mg once a day.

Plasma concentrations of SR57667 were assayed using a validated liquid chromatography tandem mass spectrometry method with a limit of quantification (LOQ) of 0.250 ng/mL.

Statistical methods:

Efficacy

Primary analysis

Primary variable: change in ^{18}F-Dopa influx constant (Ki) of the voxels of the midbrain and striatum regions from baseline to second ^{18}F-Dopa PET.

Primary efficacy analyses were performed on the intent-to-treat population (ITT) consisting of all patients who were randomized, took at least 1 dose of study medication and provided efficacy data interpretable by PET central reader from at least 1 baseline and 1 postbaseline assessment. The primary analysis was done on Ki parametric images using a voxel by voxel analysis with statistical parametric mapping (SPM) and performed on the midbrain and striatum regions by the PET central reader. The comparison was performed using analysis of covariance (ANCOVA). Results were considered as significant for nominal p values <0.05 for a cluster of at least 20 voxels, without adjustment for multiple comparisons.

As a sensitivity analysis, the primary analysis was repeated with adjustment for multiplicity using the False Discovery Rate method.

Secondary analyses

A key secondary analysis was performed on the change in ^{18}F-Dopa Ki between the 2 PET for the averaged (right+left) regions of interest, ie, the putamen and caudate, using an ANCOVA with treatment group and randomization stratum (type of dopaminergic treatment: levodopa or dopamine agonist) as fixed factors and baseline value as covariate.

For some patients, PET images were not exploitable for the SPM analysis but ^{18}F-dopa Ki values were calculated by a different method (geometric method). Consequently, there are 2 ITT populations for respectively the regions of interest and SPM analyses.

The change from baseline of the total UPDRS score (sum of scores of parts II and III) was analyzed in a mixed model on repeated measurements, with baseline as covariate, treatment, randomization stratum (levodopa or dopamine agonist), time and time x treatment as fixed factors.

Safety

The number of patients with treatment emergent adverse events (TEAEs) was summarized in each treatment group. For laboratory parameters, vital signs, and ECG parameters, descriptive statistics on raw values, changes from baseline, and number of potentially clinically significant abnormalities were provided.

Pharmacokinetics

Plasma concentrations of SR57667 were classified as:

- Plasma concentrations observed before treatment administration ($C_{trough)}$ when the data were collected in the [-4h, 0h] interval predosing or [24h, 36h] interval postdosing,
- Maximum plasma concentration ($C_{max)}$ when the data were collected in the [3h, 8h] interval postdosing.

Individual C_{max} and C_{trough} plasma concentrations were summarized by descriptive statistics separately by visit.

Summary:

Disposition and baseline characteristics:

183 patients were randomized: 88 in the placebo group and 95 in the SR57667B group. There were respectively 13 (14.8%) and 19 (20%) premature treatment withdrawals in the placebo and SR57667B groups, the most frequent reasons being investigator/subject request (respectively 4 (4.5%) and 8 (8.4%) patients) and adverse events (AEs) (respectively 4 (4.5%) and 7 (7.4%) patients).

Description of baseline characteristics is provided for the primary population of analysis, ie, the ITT population, defined as patients with a pair of baseline/end of treatment images, with respectively 78 and 74 patients in the placebo and SR57667B groups. Mean age (SD) was 61.2 (10.4) years. There were 91 males and 61 females. Mean duration (SD) of the disease since diagnosis was 1.4 (0.8) years. The dominant side was tremor in 49.3% of the patients, and rigidity/bradykinesia in 50.7%. The concomitant dopaminergic treatment was a dopamine agonist in 71.7% of patients, and L-dopa in 28.3% of the patients.

Efficacy results:

A decrease from baseline to end-of-treatment in putamen Ki was observed in both treatment groups, with SPM and regions of interest approaches. In the primary SPM analysis on the ITT population, there were no voxels with greater progression in the placebo group than in the SR57667B group ($p < 0.05$), but there were voxels with greater progression in the SR57667B group than the placebo group ($p < 0.05$). However, when corrected for multiple comparisons, the differences were no longer significant. Consistently, there was no significant difference between treatment groups in the analysis of covariance of the change from baseline to last assessment in the regions of interest analysis of the putamen Ki: mean (SD) changes were -0.00067(0.001) and -0.00072 (0.002) in the placebo and SR57667B groups, respectively.

UPDRS parts II+III scores increased in both treatment groups, with a greater increase observed in the SR57667B group than in the placebo group with no significant difference.

Safety results:

The overall frequency of TEAEs was similar in both treatment groups, as shown in the table below.

	Placebo (N=88) n (%)		**SR57667B 4 mg** (N=95) n (%)	
Patients with any TEAE (including SAEs)	78	(88.6%)	84	(88.4%)
Patients with any SAE (including SAEs leading to death)	11	(12.5%)	19	(20.0%)
Deaths	1	(1.1%)	3	(3.2%)
Patients permanently discontinuing treatment due to AE	4	(4.5%)	7	(7.4%)

More patients had serious adverse events (SAEs) or AEs leading to investigational product discontinuation in the SR57667B group than in the placebo group.

There were numerically a few more cardiac SAEs and cardiac AEs leading to treatment discontinuation in the SR57667B group than in the placebo group (8 [8.4%] patients with SAEs in SR57667B group versus none in the placebo group, and 3 [3.2%] patients with AEs leading to treatment discontinuation in the SR57667B group versus none in the placebo group).

Four patients died during the study, 1 in the placebo group and 3 in the SR57667B group. The 3 deaths in the SR57667B groups, due to respectively cardiac arrest, pulmonary embolism and aggravation of Parkinson's disease, and which all occured after more than 1.5 years into the study, were considered unrelated to study drug by the Investigator.

There were numerically more QTcF prolongations (>450 ms in males and >470 ms in females) and increases (change from baseline >60 ms) in the SR57667B group than in the placebo group, respectively 3 (3.3%) versus 1 (1.1%) and 5 (5.4%) versus 2 (2.3%). However, there were no prolongations above 500 ms, except for an isolated transient increase in 1 patient at Week 2, which returned to normal at next visit and remained normal until study end at Month 24 while treatment was continued.

Pharmacokinetic results:

After 6 months of treatment with SR57667B 4 mg once a day and up to Month 24, the geometric mean values of SR57667 C_{trough} and C_{max} range from 19.7 to 42.4 ng/mL and from 34.6 to 57.1 ng/mL, respectively.

Conclusions:

[redacted]

Date of report: 13-June-2008