Synopsis – Study 13485A

Title of Study Randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study of rasagiline in early Parkinson's disease patients not treated with levodopa in China
Investigators 15 investigators at 15 sites in China *Signatory investigator* – [redacted]
Study Centres 15 sites in China
Publications None (as of the date of this report)
Study Period *First patient first visit* – 30 March 2012 *Last patient last visit* – 17 December 2013
Objectives • *Primary Objective*: – to evaluate the efficacy of 1 mg rasagiline *versus* placebo as assessed using the change from baseline to Week 26 in the Unified Parkinson's Disease Rating Scale (UPDRS) total score in patients with early Parkinson's disease not treated with levodopa • *Secondary Objectives*: – to evaluate the effect of rasagiline *versus* placebo on: • the change from baseline to Week 26 in the subscale scores of the UPDRS (parts I, II, and III) • time to onset of levodopa therapy • levodopa administration during the 26-week treatment period – to evaluate the safety and tolerability of rasagiline *versus* placebo • *Exploratory Objectives*: – To evaluate the effect of rasagiline *versus* placebo on: – response, defined as a categorical change from baseline to Week 26 in the UPDRS total score – the change from baseline in UPDRS total score and UPDRS subscale scores at each visit – Clinical Global Impression – Severity of Illness (CGI-S) score and Clinical Global Impression – Global Improvement (CGI-I) score – Parkinson's Disease Questionnaire (PDQ-39) scores at Weeks 14 and 26 – EuroQol questionnaire (EQ-5D) utility index at each visit – resource use collected using the Health Economic Assessment questionnaire for Parkinson (HEA Parkinson) at Weeks 14 and 26
Methodology • This was an interventional, multi-site, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study. • The study consisted of a 4-week Screening Period, a 26-week double-blind treatment period with rasagiline or placebo once daily (patients were randomised in a 1:1 ratio), and a 4-week Safety Follow-up period. • Efficacy and safety data were collected throughout the study.

Number of Patients Planned and Analysed

- A total of 130 patients were planned for randomisation: 65 in the placebo group and 65 in the rasagiline group
- Patient disposition is summarised below:

	Placebo		Rasagiline 1mg	
	n	(%)	n	(%)
Patients randomised	65		65	
Patients treated (all-patients-treated set [APTS]):				
Patients completed	53	(81.5)	58	(89.2)
Patients withdrawn	12	(18.5)	7	(10.8)
Primary reason for withdrawal:				
Adverse event(s)	5	(7.7)	3	(4.6)
Protocol violation	0	(0.0)	3	(4.6)
Withdrawal of consent	7	(10.8)	1	(1.5)
Analysis sets:				
APTS	65		65	
Full-analysis set (FAS)	63		64	
Per-protocol set (PPS)	49		55	

Diagnosis and Main Inclusion Criteria

Outpatients with a primary diagnosis of idiopathic Parkinson's disease, who:

- had ≥2 of the cardinal signs of Parkinson's disease (resting tremor, bradykinesia, rigidity) without other known or suspected cause of parkinsonism
- had a Modified Hoehn and Yahr Staging Scale score <3 at screening and baseline
- were ≥35 years of age
- could stay for 26 weeks on placebo treatment at the time of study enrolment, based on the investigator's best judgement
- did not take or required antiparkinsonian medications, except anticholinergics
- had not taken levodopa, dopamine agonists, or amantadine for ≥42 days prior to baseline

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number

Rasagiline – 1 mg/day; tablets, orally; batch No. R14269

Duration of Treatment

26 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo – tablets, orally; batch No. PLR001

Efficacy Assessments

- *Primary variable*:
  - United Parkinson's disease rating scale (UPDRS) total score (sum of the subscale scores for Part I to III)
- *Secondary variables*:
  - UPDRS subscale scores Parts I to III
  - need for levodopa therapy
- *Exploratory variables*:
  - CGI: CGI-S and CGI-I scores
  - pharmacoeconomics: PDQ-39, EQ-5D scores, and HEA Parkinson

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), and physical (including a detailed skin examination) and neurological examinations.

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the primary efficacy variable
  - *per-protocol set* (PPS) – all patients in the FAS who completed 26 weeks of treatment without any major protocol violations; major protocol violations were defined as:
    - drug compliance <70% during the 26-week treatment period
    - drug compliance <80% between Weeks 20 and 26
    - the use of disallowed concomitant medication during the study
    - the washout period for levodopa, dopamine agonists, amantadine or antidepressants (including selective serotonin reuptake inhibitors, tricyclic, and tetracyclic antidepressants) was <42 days prior to baseline
    - the washout period for selegiline was <90 days prior to screening
    - a change in the dose of anticholinergics concomitantly administered post-randomisation
    - the patient had taken IMP from a wrongly assigned IMP kit due to dispensing errors
    - the use of sedative drugs which were allowed for periodic use but were administered on the day of assessment
- The primary analysis was the change from baseline to Week 26 in UPDRS total score. Treatment difference between the rasagiline and placebo groups was compared using an analysis of covariance (ANCOVA), with treatment and site as fixed factors, and baseline UPDRS total score as a covariate, using last observation carried forward (LOCF). If the estimated treatment difference was in favour of rasagiline for the two-sided test at the 25% level of significance, a positive trend was shown.
- As a sensitivity analysis, the primary endpoint was analysed using a mixed model for repeated measurements (MMRM), which included a fixed effect of site and visit, treatment-by-visit interaction, and baseline-by-visit interaction using an unstructured covariance matrix. The primary endpoint was also analysed on the PPS and by an ANCOVA model based on the FAS with observed cases (OC).
- The secondary endpoints were analysed by an ANCOVA model using LOCF with treatment and site as fixed factors and the corresponding baseline UPDRS subscale score as a covariate.
- If >10% of the patients had taken levodopa during the treatment period, time to onset of levodopa treatment and levodopa treatment within 26 weeks were analysed.
- Response (defined as a worsening of <3 points in UPDRS total score from baseline to Week 26) was analysed using logistic regression, with treatment and site as factors, and baseline UPDRS total score as a covariate, using LOCF. The changes from baseline in UPDRS total score at each visit were analysed by an MMRM model similar to that for the primary efficacy analysis. The change from baseline to Week 26 in CGI-S score and the CGI-I score at Week 26 were analysed by an ANCOVA model using LOCF, with treatment and site as fixed factors, and the baseline CGI-S as a covariate.
- Descriptive statistics of absolute scores and changes from baseline are presented for EQ-5D and PDQ-39. The change from baseline to Week 26 in EQ-5D utility index and visual analogue scale (VAS) and the change from baseline to Weeks 14 and 26 in PDQ-39 scores (PDQ-39 dimensions and PDQ-39 SI) were analysed by ANCOVA using OC and LOCF, with treatment and site as fixed factors and the respective baseline score as a covariate. The variables for HEA Parkinson were summarised using descriptive statistics (FAS, OC).
- The overall incidences of adverse events, SAEs, and adverse events leading to withdrawal were summarised for each treatment group. The incidences of pre-treatment adverse events, TEAEs, treatment-emergent SAEs, and adverse events leading to withdrawal were summarised by system organ class (SOC) and preferred term. TEAEs with an incidence ≥5% in either treatment group were summarised by preferred term. Adverse events reported more than once in the same patient were counted only once in a period, and at the maximum intensity reported. The incidences of TEAEs were also summarised by preferred term and intensity and causality categories for each treatment group.

Statistical Methodology (continued)

- Absolute values and changes from baseline to the last assessment in clinical safety laboratory tests, vital signs, and weight/BMI were summarised by visit and last assessment using descriptive techniques. Potentially clinically significant (PCS) values were flagged and tabulated. ECG status was summarised by counts and percentages.

Demography of Study Population

- The treatment groups were similar with respect to age, weight, and BMI, but not sex distribution. There was a lower proportion of men in the rasagiline group than in the placebo group (54% *versus* 62%).
- The baseline efficacy variables are summarised below (FAS):

	Placebo (N = 63) Mean±SD	Rasagiline 1mg (N = 64) Mean±SD
UPDRS total score	28.6±15.3	26.1±11.7
UPDRS Part I subscale score (UPDRS mentation)	1.5±1.6	1.6±1.4
UPDRS Part II subscale score (UPDRS-ADL)	7.9±4.6	7.2±3.3
UPDRS Part III subscale score (UPDRS motor)	19.1±10.6	17.3±8.7
CGI-S score	3.1±0.7	3.2±0.6

- There were no clinically relevant differences in the mean baseline efficacy values between the treatment groups

Efficacy Results

- In the primary efficacy analysis, the decrease in the mean UPDRS total score was greater in the rasagiline group than in the placebo group (-3.2 points *versus* -0.2 points, respectively). The mean difference to placebo was statistically significant (-3.0 points; p = 0.0254 [FAS, ANCOVA, LOCF]).
- The mean UPDRS mentation score increased slightly in the placebo group, but decreased (improved) in the rasagiline group; the mean difference to placebo was statistically significant (-0.6 points; p = 0.003 [FAS, ANCOVA, LOCF]).
- The mean UPDRS-ADL score increased in the placebo group and decreased (improved) in the rasagiline group; the mean difference to placebo was numerically in favour of rasagiline (-0.7 points, p = 0.196 [FAS, ANCOVA, LOCF]).
- The mean UPDRS motor score decreased (improved) in both treatment groups; the improvement was greater in the rasagiline group than in the placebo group. The mean difference to placebo was numerically in favour of rasagiline (-1.7 points, p = 0.064 [FAS, ANCOVA, LOCF]).
- As ≤10% of the patients had taken levodopa during the treatment period, time to onset of levodopa treatment and levodopa treatment within 26 weeks were not analysed.
- The proportion of responders was higher in the rasagiline group than in the placebo group (80% *versus* 67%, respectively); the odds ratio was numerically in favour of rasagiline (FAS, logistic regression, LOCF).
- The mean UPDRS total score improved in both treatment groups; the mean difference to placebo was statistically significant at Weeks 4 and 26 and numerically in favour of rasagiline at the other timepoints (FAS, MMRM, OC).
- The mean CGI-S score worsened slightly in the placebo group but remained relatively unchanged in the rasagiline group; the mean difference to placebo was numerically in favour of rasagiline (FAS, ANCOVA, LOCF).
- The mean CGI-I score worsened slightly in the placebo group but remained unchanged in the rasagiline group; the mean difference to placebo was numerically in favour of rasagiline (FAS, ANCOVA, LOCF).
- In general, the mean score for each PDQ-39 dimension and the summary index increased (worsened) in both treatment groups, except for *Cognition*, *Emotional Well-being*, and *Stigma* in the rasagiline group, which decreased (improved). The treatment differences to placebo were numerically in favour of rasagiline for all PDQ-39 dimensions except *Bodily Discomfort*, which was numerically in favour of placebo (ANCOVA, OC and LOCF).

Efficacy Results (continued)

- The EQ-5D health state improved in the rasagiline group but deteriorated in the placebo group; the difference to placebo was statistically significant (FAS, ANCOVA, OC and LOCF). The EQ-5D utility index deteriorated to a smaller extent in the rasagiline group than in the placebo group; the difference to placebo was numerically in favour of rasagiline (FAS, ANCOVA, OC and LOCF).
- The patients' socio-demographic status and resource use profile were assessed using the HEA Parkinson questionnaire. In both treatment groups, the majority of the patients lived with their partners and approximately two-thirds of the patients did not have a caregiver (70% and 67% in the placebo and rasagiline groups, respectively); very few patients (total of 3 patients from both treatment groups) were on long-term sick leave. The proportion of patients who were employed was comparable (29% and 31% in the placebo and rasagiline groups, respectively). In general, the profile for resource use was similar in the treatment groups.

Safety Results

- The adverse event incidence is summarised below:

	Placebo		Rasagiline 1mg	
	n	(%)	n	(%)
Patients treated	65		65	
Patients who died	0		0	
Patients with serious AEs (SAEs)	4		0	
Patients with treatment-emergent AEs (TEAEs)	30	(46.2)	27	(41.5)
Patients with AEs leading to withdrawal	5	(7.7)	3	(4.6)
Total number of TEAEs	53		59	
Total number of SAEs	5		0	

- The overall incidence of treatment-emergent adverse events was slightly lower in the rasagiline (42%) than in the placebo group (46%). A total of 8 patients withdrew due to adverse events: 5 (7.7%) patients in the placebo group and 3 (4.6%) patients in the rasagiline group.
- No deaths occurred during the study. In the treatment period, 4 patients (placebo group only) had one or more SAEs. The SAEs were isolated cases reported in single patients. All the SAEs were considered *not related* to IMP by the investigator.
- For the majority of the patients with TEAEs, the events were *mild* or *moderate*. The incidence of *mild* TEAEs was higher in the placebo group than in the rasagiline group (32% *versus* 17%, respectively); the incidence of *moderate* TEAEs was lower in the placebo group than in the rasagiline group (11% *versus* 25%, respectively). Two patients (both in the placebo group) had *severe* TEAEs. In patients who had related TEAEs, the events were either *mild* or *moderate*.
- The TEAEs with an incidence ≥5% in either treatment group were *accidental overdose* (placebo: 4.6%; rasagiline: 6.2%) and *Parkinson's disease* (placebo: 6.2%; rasagiline: 7.7%).
- There were no clinically relevant differences in the clinical safety laboratory values, vital signs, weight, or ECG status between the treatment groups.

Conclusions

- The primary efficacy analysis showed that rasagiline 1 mg reduced the UPDRS total score statistically significantly more than placebo in Chinese patients with early Parkinson's disease.
- In the secondary and exploratory efficacy analyses (assessing activities of daily living, motor function, global improvement, and response), the improvements were numerically in favour of rasagiline. However, the improvement in mentation in the rasagiline group was statistically significant compared with placebo.
- The improvement in quality of life was numerically in favour of rasagiline except for *bodily discomfort*, which was numerically in favour of placebo. The improvement in health state in the rasagiline group was statistically significant compared with placebo.
- Rasagiline was safe and well tolerated and no new safety concerns were observed in Chinese patients.

Date of the Report

8 May 2014

This study was conducted in compliance with the principles of *Good Clinical Practice*.