1. SYNOPSIS – ABBREVIATED REPORT

Name of Sponsor/Company: Teva Global Branded Products R&D, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: AZILECT® 1 mg tablets	**Volume:**	
Name of Active Ingredient: rasagiline mesylate	**Reference:**	

Title of Study: An Open-Label, Multi-Center, Follow-Up Study Designed to Evaluate the Long-Term Effects of Rasagiline in Parkinson's Disease Subjects who Participated in the ADAGIO Study

Investigators and Study Centers: Principal investigators were Dr. Robert Hauser MD, Prof. Warren Olanow MD, Prof. Olivier Rascol MD, and Prof. Fabrizio Stocchi MD. Subjects were enrolled at 102 study centers in 13 countries (Argentina, Canada, France, Germany, Hungary, Israel, Italy, Netherlands, Portugal, Romania, Spain, United Kingdom, United States).

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 20 Jul 2009 to 28 Feb 2013 **Phase of Development**: 4

Objectives: The objectives of the study were:

- To investigate whether the effect of early-start rasagiline treatment (according to the ADAGIO study protocol) provided long term benefits over delayed-start.
- To investigate the long-term effects of rasagiline in PD subjects who participated in the ADAGIO study and have continued on rasagiline treatment.

Number of Subjects (Planned and Analyzed): This was a follow-up study of the TVP-1012/500 (ADAGIO) study, which planned to include PD patients who entered the active phase of the study TVP-1012/500. The maximal sample size for this study was 1091, which is the number of subjects who entered the active phase of the study TVP-1012/500. A total of 683 subjects were enrolled into the study (331 delayed-start, 352 early-start) and received at least 1 dose of study treatment.

Diagnosis and Main Criteria for Inclusion: Patients were included in the Core follow-up period if all of the following main criteria were met (not all inclusive):

- Subjects who participated in the ADAGIO study, and who entered the active phase of the study
- Subjects who are currently on rasagiline treatment (or subjects who have stopped rasagiline treatment, are willing to restart treatment, and in the opinion of the investigator will gain clinical benefit from restarting treatment)

- Subjects with a diagnosis of PD
- Subjects willing and able to give written informed consent

Patients were included in the Extended follow-up period if all of the following main criteria were met (not all inclusive):

- Subjects who completed the Core follow-up study period (whether they are on rasagiline treatment or not)
- Subjects with a diagnosis of Parkinson's disease at the Core termination visit (Visit 9, Month 24)
- Subjects willing and able to give written informed consent

Main Criteria for Exclusion: Patients were excluded from participating in the Core follow-up period if 1 or more of the following main criteria were met (not all inclusive):

- Subjects who have discontinued rasagiline treatment due to an AE and have not restarted rasagiline treatment subsequently.
- Subjects who cannot be given rasagiline due to any exclusion based on the local label (including pregnancy or nursing women) or due to the use of medications contraindicated for concomitant use with rasagiline according to local label.
- Subjects with a medical condition that is considered by the investigator as significant enough to prevent participation

Patients were excluded from participating in the Extended follow-up period if 1 or more of the following main criteria were met (not all inclusive):

- Subjects with a medical condition that is considered by the investigator as significant enough to prevent participation in the extended follow-up study
- Subjects who can no longer be given rasagiline due to any emergent exclusion based on the local label (including pregnancy or nursing women) or due to the new use of medications contraindicated for concomitant use with rasagiline according to local label (for subjects who are still on rasagiline at Visit 9)

Study Drug Dose, Mode of Administration, and Administration Rate and Batch Number: Subjects were treated with an oral daily dose of one AZILECT® (rasagiline mesylate) 1 mg tablet. The study was conducted with commercially available AZILECT® drug product, with recording of the batch numbers used. AZILECT® is indicated for the treatment of idiopathic Parkinson’s disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations.

Method of Blinding: Not applicable.

Duration of Treatment: 24 months (Core follow-up study) followed by an additional 12 months (Extended follow-up study)

General Design and Methodology: Eligible subjects, who participated in the ADAGIO trial and who sign an approved informed consent form, were to be enrolled into the study by their original centers. Subjects who had stopped rasagiline therapy and in the opinion of the investigator would gain clinical benefit from restarting treatment could also be considered for enrollment in the Core follow-up study period. Use of any other anti-PD treatment was permitted as deemed necessary by the treating physician (according to the subject's clinical status).

During the Core follow-up period, subjects were to continue to receive 1 mg rasagiline once a day. During the Extended follow-up study period, only subjects who were still on rasagiline at Visit 9 were to continue to receive treatment with rasagiline 1 mg per day. Tablets were supplied by the Sponsor and given according to the local label. Study drug was to be dispensed every 3, 6, or 12 months (as permitted and decided at each site). The study drug could be dispensed either at the site or via mail using a 'mail order' supply service where this was possible. Subjects who stopped rasagiline treatment during the study were to continue to be followed as per the protocol (according to their willingness).

Assessment of outcome measures was conducted every three months in two visit types, as follows:

Short visits – Scheduled visits were at Study Months 3, 6, 9, 15, 18, 21, 27, 30 and 33. Short visits could be conducted either over the phone or as on-site visits at the discretion of the investigator. The following data were collected at each short visit:

- Adverse events (AE), only for subjects who are still on rasagiline at the time of the visit. AE were to be recorded in source documents for all subjects whether they are on rasagiline or not, during the entire duration of the study.
- Rasagiline use, including dose and frequency
- Concomitant medications/treatments:
  - PD medications including dose and frequency
  - Placement of deep brain stimulation (DBS) device or an ablative procedure on a central nervous system structure for treatment of PD-related symptoms
  - Antidepressant use including dose and frequency
- PD functional status: loss of balance, falls, freezing of gait (FOG), dyskinesias, hallucinations, cognitive decline in a manner that impairs daily function (memory decline, difficulty in concentration, difficulty in performing complex tasks (e.g. cooking, shopping, household chores), difficulty in working with electrical appliances, difficulty in using everyday items (e.g. comb, toothbrush, cutlery etc.), difficulty in outdoor orientation), and functional decline (unemployment, the use of walking aids, the need for a caregiver, nursing home placement)
- Quality of life (QoL): Total Functional Capacity (TFC) scale, Parkinson's Disease Questionnaire of Quality of Life (PDQ8), EuroQol 5 domain questionnaire (EQ-5D).

Long visits – Long visits were conducted at the baseline visit of the Core follow-up study period and every 12 months at the study site for all subjects. Scheduled visits were at Study Month 0, 12, 24, and 36. The long visits had

to be conducted at the site. For subjects who experience ON/OFF fluctuations, efforts were to be made to perform assessments during the ON state. Assessments included the following:

All assessments performed during the short visits. AEs were to be recorded only for subjects who are on rasagiline at the time of the visit. AEs were to be recorded in source documents for all subjects whether they are on rasagiline or not, during the entire duration of the study.

- Confirmation of diagnosis of PD (using a PD diagnosis form)
- Hoehn and Yahr stage
- Unified PD Rating Scale (UPDRS) 3.1
- UPDRS Version 4, part 1 (Experiences of Daily Living [EDL] Scale)
- The Montreal Cognitive Assessment (MoCA) scale
- Parkinson Fatigue Scale
- Non-motor symptom questionnaire (NMSQ) of the Parkinson Disease Society

Visit 9/Month 24 served also as the baseline visit for the Extended follow-up study period. At Visit 9 (Month 24), the subject's eligibility to participate in the Extended follow-up study period was reviewed and eligible subjects were to be thoroughly informed about the full aspects of the study extension, including scheduled visits and activities. Subjects had to sign the addendum to the EC/IRB approved informed consent form in order to participate in the Extended follow-up study period. For eligible subjects who decided not to participate, the reason was to be recorded in the eCRF. All these activities had to be recorded in the Baseline Extended follow-up visit.

Subjects who were still on rasagiline treatment at Visit 9 were provided with rasagiline study medication for the next 3 or 12 months (depending on the study medication dispensing frequency at the site).

Outcome Measures: The main outcome analysis was the emergence of the following milestones since the last assessment (short or long visit) per subject report:

- Unsteady gait and balance
- Falls
- FOG
- Cognitive decline (at least two positive answers for the cognitive function questions)

Additional analyses included the emergence of the following milestones since the last assessment (short or long visit) per subject report:

- Time to treatment:
  - Dopaminergic treatment
  - Levodopa

  - Surgery for PD

- Dyskinesias
- Hallucinations
- Functional decline:
  - Employment status
  - The use of walking aids
  - The need for a caregiver
  - Nursing home placement

The following were also to be analyzed:

- UPDRS, total and sub-scores, version 3.1
- UPDRS Version 4, part I (EDL Scale)
- Hoehn and Yahr scale
- Parkinson Fatigue Scale
- MoCA Scale
- Non motor symptom questionnaire of the Parkinson disease society
- QoL: TFC, PDQ8, and EQ-5D

Descriptive statistics were applied to all outcome measures.

Safety Variables: Safety was assessed by adverse events (including deaths, serious adverse events, and withdrawals due to adverse events) and tolerability (failure to complete the study).

Summary of Results and Conclusions

This was an open-label, multi-center, uncontrolled follow-up study to the ADAGIO trial.

The objectives of the study were:

- To investigate whether the effect of early-start rasagiline treatment (according to the ADAGIO study protocol) provided long term benefits over delayed-start.
- To investigate the long-term effects of rasagiline in PD subjects who participated in the ADAGIO study and have continued on rasagiline treatment.

The maximal sample size for this study was 1091, which is the number of subjects who entered the active phase of the ADAGIO trial (TVP-1012/500). Data from 683 subjects who entered this study (72% of ADAGIO active phase completers) were analyzed.

Median exposure to rasagiline in this study was 35.6 months (range 0 to 38.6 months).

For this abbreviated report, the efficacy results summarized here are not all of those planned in the protocol and also include results from exploratory analyses. All of the results summarized here present data from on-treatment only (ie, does not include the FU visit in case the patient discontinued treatment but continued to come to the FU visits). For exploratory analyses, the difference between the early- and delayed-start groups for the time to milestones was assessed using the log-rank test.

The main outcome analysis was emergence of unsteady gait and balance, falls, freezing of gait, and cognitive decline. At study baseline, mean duration of PD was 46.9 months and total-UPDRS was 25.6 units; 88% of patients were on rasagiline and 26% had been maintained on rasagiline monotherapy.

Results indicated that there were no significant differences in time to any milestone between subjects who were in the early-start group vs. those in the delayed-start group. During the 3-year study, 43.6% of subjects (total population) had occurrence of unsteady gait and/or balance impairment; 35.7% had fallen; 26.2% had occurrence of FOG; and 33.1% had cognitive decline.

Additional analysis included the emergence of time to dopaminergic treatment, time to levodopa, surgery for PD, dyskinesias, hallucinations, functional decline in employment status, use of walking aids, need for caregiver, nursing home placement. At baseline, 164 (24%) patients were on rasagiline monotherapy; 277 patients (40.6%) received additional dopamine agonist therapy and 297 patients (43.5%) received additional levodopa. During the 3-year study, 75 (11%) of patients received additional dopamine agonist therapy, 184 (26.9%) received additional levodopa, and 7 (1%) underwent PD surgery.

During the study, 23.7% of patients had emergence of dyskinesia; 14.5% had emergence of hallucinations; 11.9% reported employment status worsening; 15.8% required a new walking aid; 6.7% reported a new need for a caregiver and 3.4% had worsening of residential status.

Mean baseline Total-UPDRS score was 25.6 ± 12.3 units; UPDRS-motor score was 17.4 ± 8.8 units; and UPDRS-ADL score was 7.0 ± 4.2 units. At the end of the study, patients had worsened by a mean of 6.0 ± 11.6 units on the Total-UPDRS, 3.3 ± 8.6 units on the UPDRS-motor subscale and 2.0 ± 4.0 units on the UPDRS-ADL subscale.

Given the uncontrolled nature of the study, safety conclusions must be drawn with caution. However, the proportion of subjects with AEs (85.1%), SAEs (25.0%), and AEs leading to discontinuation of rasagiline (4.7%) are consistent with the rates expected in a population of PD subjects. The AE profile is consistent with the known AE profile for rasagiline in PD patients.

Thirteen subjects died during the study. None of the deaths were assessed as related to rasagiline and only a single death was assessed as related to PD.

In conclusion, there was no evidence that early-start rasagiline treatment (according to the ADAGIO study protocol) provided long-term benefits over delayed-start. However, there was, on average, a 2.5-year gap following the end of ADAGIO to the start of this follow-up study and this was associated with substantial drop-out such that the two

groups were no longer statistically comparable, which may have compromised the ability to detect a long-lasting effect. Long-term treatment with rasagiline in this follow-up study raised no new safety concerns. The results of this study do not impact on the current Azilect® prescribing information.

As this study was not controlled and as no significant differences in time to any milestone were observed between the early-start group vs. those in the delayed-start group, an abbreviated clinical study report has been prepared, focussing on safety and including a brief summary of the main efficacy results.

Date of report: 23 May 2014