TEVA BRANDED
PHARMACEUTICAL
PRODUCTS R&D, INC.

AZILECT® (RASAGILINE MESYLATE) FOR SLOWING CLINICAL PROGRESSION IN PATIENTS WITH IDIOPATHIC PARKINSON'S DISEASE

BRIEFING DOCUMENT FOR THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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Abbreviations

AC	Active Control
ACTE	**ACT**ive **E**fficacy data analysis set
ADAGIO	**A**ttenuation of **D**isease Progression with **AGI**LECT®/ AZILECT® **O**nce-daily
ADL	Activities of Daily Living
AD	Alzheimer's Disease
AE	adverse event
AIR	Advise/Information Request
ALP	alkaline phosphatase
ANCOVA	Analysis of covariance
AST	aspartate transaminase
AT	Active Treatment
AUC	area under the curve
BUN	blood urea nitrogen
CI	Confidence Interval/s
C_{max}	maximum plasma concentration
CCDS	Company Core Data Sheet
CO	Completers data analysis set
COMT	catecholamine-o-methyl transferase
CoQ10	Coenzyme Q10
CYP	cytochrome
DAT	striatal dopamine transporter
DBP	diastolic blood pressure
DS	Delayed Start, i.e. patient received placebo in the PC phase
ECG	Electrocardiogram
ES	Early Start, i.e. patient received rasagiline in the PC phase
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration
GDNF	glial cell-derived neurotrophic factor
GGT	gamma glutamyl transpeptidase
H&Y	Hoehn and Yahr
HLT	Higher Level Term
ICH	International Conference on Harmonisation

ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intent-to-Treat
LOCF	Last-Observation-Carried-Forward
LOV	Last Observed Value
LUC	large unstained cells
LSM	Least Square Means
MAO	Monoamine Oxidase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRI	Magnetic resonance imaging
NA	not applicable
NDA	New drug application
Nec	Not elsewhere considered
NF-κB	Nuclear factor kappa B
NGF	nerve growth factor
NHE	Natural History Estimate
NHSS	Natural History Staggered Start
NOS	not otherwise specified
NS	not significant
P	placebo
PC	Placebo-controlled
PCS	Potential Clinical Significance
PD	Parkinson's Disease
PP	Per Protocol data analysis set
PT	Preferred Term
PTP	permeability transition pore
QTc	Corrected QT interval
QTcB	QTc corrected by Bazett's formula
QTcF	QTc corrected by Fredericia's formula
RBC	red blood cell
RMA	Repeated Measures Analysis
ROW	rest of the world
RW	randomized withdrawal
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure

sNDA	Supplemental new drug application
SNpc	Substantia Nigra pars compacta
SNRI	serotonin-norepinephrine reuptake inhibitor
SPA	Special Protocol Assessment
SPC	Summary of Product Characteristics
SSRI	selective serotonin reuptake inhibitor
T_{max}	time to maximum concentration
TEMPO	**T**VP-1012 in **E**arly **M**onotherapy for **P**D **O**utpatients
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
vs	versus
WBC	white blood cell

1.0 Executive Summary

Azilect® (rasagiline mesylate), is a potent, selective, and irreversible monoamine oxidase type B (MAO-B) inhibitor that was initially approved (0.5 and 1 mg once daily) by the Food and Drug Administration (FDA) in May 2006 for the treatment of signs and symptoms of Parkinson's disease (PD). Teva is now seeking additional approval to market Azilect® 1 mg to slow the clinical progression of idiopathic PD. There are no other approved PD medications that slow clinical progression. Thus, there is substantial unmet medical need for treatments that can slow the progressive course of PD.

Teva sponsored the TEMPO (**T**VP-1012 in **E**arly **M**onotherapy for **P**D **O**utpatient) clinical trial to study the symptomatic effect of 1 mg and 2 mg rasagiline as monotherapy and the findings from TEMPO were included in the initial NDA. The second pre-planned phase of TEMPO, was structured as a delayed-start design to compare earlier versus delayed treatment to see if rasagiline slowed disease progression. Given the encouraging findings from TEMPO, Teva, with FDA input, designed the ADAGIO (**A**ttenuation of **D**isease **P**rogression with **AGI**LECT®/AZILECT® **O**nce-daily), as a delayed-start design, clinical trial to confirm the beneficial effect on clinical progression observed in TEMPO.

Both TEMPO and ADAGIO were designed as delayed-start clinical trials differing in the length of follow-up and hypotheses tested but using the same clinical endpoint (Unified Parkinson's Disease Rating Scale [UPDRS]). The purpose of the delayed treatment arm is to allow separation of symptomatic effects from the beneficial effect of slowing disease progression. If rasagiline only has a symptomatic effect, patients that have a delay in treatment should simply "catch up" to those that are treated earlier: differing only in when they achieve the symptomatic effect. However, if the delayed treatment group does not catch up to the early treatment group, then the progression of disease was slowed by earlier treatment.

TEMPO consisted of a 26-week, placebo-controlled period followed by a double-blind, 26-week extension of all active treatment. Those initially started on rasagiline represent the early treatment group ("early start") and those that are randomized to placebo and then rasagiline in the second phase are the delayed treatment group ("delayed start"). ADAGIO also consisted of the same two phases, but each phase was 36 weeks in length. Thus, TEMPO was a 52-week, delayed-start study while ADGAIO was 72 weeks.

TEMPO found that patients who started on rasagiline 2 mg at the beginning of the study had less deterioration in their UPDRS score at 52 weeks than patients assigned to a 26-week delay in treatment. Thus, patients assigned to a delay in treatment for 2 mg did not "catch up" as would be expected if rasagiline's effect was only symptomatic in nature. TEMPO did not include a delayed-treatment group for 1 mg. However, when compared to the 2 mg delayed-treatment group, the early start 1 mg group deteriorated less.

FDA assisted in the design of ADAGIO and offered suggestions for the study's analysis. However, the use of the delayed-start design is a relatively new approach and the thinking regarding this design and its analyses has evolved over time. Therefore, there were changes made over the course of the trial based on discussions between FDA and Teva to determine the appropriate set of primary hypotheses to test. In the initial statistical analysis plan (SAP) submitted to FDA (March 2007), there were two hypotheses on which ADAGIO study power was based and from here on out will be defined as "original hypotheses".

Original Hypotheses

1) If the early start-group had a reduced rate of progression, then after the delayed start group has experienced a symptomatic effect and continued treatment (assumed by 12 weeks from delayed treatment onset at Week 48) the UPDRS change should be lower at 48-72 weeks in the early-start group than in the delayed-start group.

2) The rate of progression should be the same (non-inferior) once the delayed-start group has experienced a symptomatic effect and continues treatment, i.e. the slopes of total UPDRS change over time for the early- and delayed-start groups should not be converging.

In October 2007, the FDA recommended that three hypotheses be used to test for disease modification. These three hypothses are designated from here on out as the "final hypotheses"and are as follows:.

Final Hypotheses

1) The rate of progression after the initial symptomatic effect should be less with rasagiline than placebo, i.e. the rate of progression is manifested by the slope, thus the slope of total UPDRS change over time for the study drug group should be smaller than that for the placebo group.

2) If the early-start group had reduced rate of progression the UPDRS change should be lower at 72 weeks in the early-start group than in the delayed-start group.

3) The rate of progression should be the same (non-inferiority) once the delayed-start group has a symptomatic effect and continues treatment, i.e. the slopes of total UPDRS changes over time for the early- and delayed-start groups should not be converging.

Teva's adoption of FDA's recommendations reduced the power of the ADAGIO study to distinguish between delayed and early start change from baseline to Week 72 in UPDRS scores by 15 percentage points (from 87% to 72%); a substantial impact on study power. Because the recommendation was made 11 months after the last patient enrolled in ADAGIO, there was no opportunity for TEVA to add patients

to compensate for the lost statistical power. It is important to be mindful of this fact when assessing the non-significant p-value (0.0506) obtained for the difference between early and delayed treatment with 1mg in UPDRS change at Week 72 in the final SAP specified analysis.

The findings in ADAGIO based upon the recommended analysis that was adopted in the final SAP for the study are as follows:

For both 1 mg (-0.046; 95% CI: -0.083, -0.010; p=0.0133) and 2 mg (-0.072; 95% CI: -0.109, -0.036; p=0.0001), the slope of UPDRS (measured as UPRDS per week) over 12 to 36 weeks of the placebo-controlled phase was significantly smaller than with placebo, suggesting an effect on clinical progression (Hypothesis #1).

At Week 72, using the combined dataset of both 1 mg and 2 mg data from the final SAP, the change from baseline in UPDRS was smaller for the group assigned 1 mg at the start of study compared to the group assigned a 36-week delay in receiving 1 mg (-1.425; 95% CI: -2.853, 0.004; p=0.0506) (Hypothesis #2).

For 2 mg, there was no difference between the early-start and delayed-start groups (0.179; 95% CI: -1.218, 1.576) (Hypothesis #2).

For both 1 and 2 mg, the delayed- and early-start group had similar slopes over the 48 to 72 week period (Hypothesis #3).

Because of interactions found for the pre-specified statistical model used for Hypothesis #2, an alternative statistical model based upon separate comparison of each dose group with the corresponding control group (delayed-start) supported the findings for a difference between early- and delayed-start of 1 mg (-1.680; 95% CI: -3.148, -0.212; P = 0.025). At the time, the separate datasets option was chosen as the preferred one and the most appropriate way to analyze the data for Hypotheses #2 and #3, since it preserved the original model structure that was defined in the SAP.

Moreover, analyses performed on the original Hypothesis #2 showed a similar effect for 1 mg (-1.408; 95% CI: -2.500, -0.317;P = 0.012). Sensitivity and supportive analyses for the 1 mg dose were all consistent with the primary analyses, and they all supported a beneficial effect of early treatment with 1 mg.

The ADAGIO testing paradigm using the new hypotheses was also applied to the TEMPO dataset, although this analysis was under powered. Using this approach, the findings of 2 mg in TEMPO were consistent with the original analyses suggesting that there was beneficial slowing in progression of PD. In the long-term extension of TEMPO, efficacy was assessed for patients treated with rasagiline as monotherapy, or as an adjunct to other PD medications as needed, for up to 6.5 years. These data suggest

that the benefit of early treatment persists. Finally, a combined analysis of both TEMPO and ADAGIO was conducted using the Natural History Staggered Start (NHSS) model. In this model, both 1 and 2 mg doses supported a benefit of early over delayed treatment.

Accordingly, Teva believes that the evidence obtained with the 1 mg dose group from ADAGIO is robust and supported by the evidence obtained from TEMPO. The failure of the 2 mg in ADAGIO is perplexing since there was clear separation of the slopes early in the study for 2 mg (Hypothesis #1) and since the 2 mg dose in TEMPO had strong support.

One possible explanation for failure of the 2 mg dose in ADAGIO is that the disease-modifying effect of the 2 mg dose was masked due to a robust or prolonged symptomatic benefit during the second phase. With the mild PD symptoms of the population in ADAGIO (mean baseline UPDRS, 20 points) it is possible that differences could not be detected because of a "floor effect" in the UPDRS scale. If this floor effect exists, one may expect an effect on clinical progression to be demonstrable in a subset of patients with more advanced disease. Indeed, a post-hoc analysis by baseline UPDRS scores demonstrated a pronounced benefit (-3.63) of early 2 mg vs. delayed 2 mg treatment on the change from baseline to Week 72 in patients with the baseline UPDRS scores (>25.5). Another possible explanation is the impact of dropouts and patients who transferred early to the active-treatment phase that occurred more frequently in the delayed-start groups.

In summary, two independent double-blind studies, TEMPO and ADAGIO, found a beneficial effect of early treatment with rasagiline as compared to delayed treatment and provide the basis for independent substantiation of these findings. In particular in ADAGIO, the approximately 1.7 units reduction in progression of the UPDRS symptom score translates to a clinically meaningful 38% reduction in clinical progression for the 1 mg, which could be even more important over the long term. This clinical benefit cannot be explained by symptomatic effect only.

The safety profile observed in ADAGIO is consistent with current labeling and there are no new issues that have emerged in the post-marketing experience.

The benefit and risk evaluation is substantially in favor of approval of the 1 mg dose to slow the clinical progression of PD. Inclusion of this information in the Azilect® label is essential to ensure that the treating physicians and their PD patients have full and complete access to the most current information that describes the benefits of Azilect® therapy.

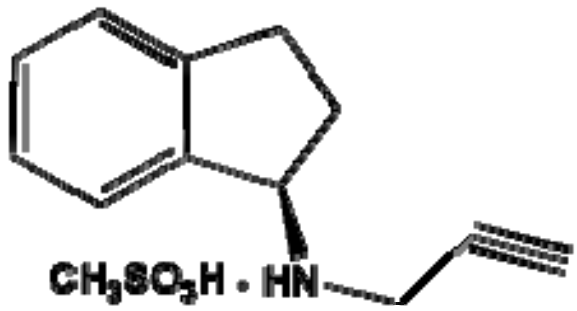
2.0 Introduction

2.1 Overview of Rasagiline

Teva is seeking marketing approval for Azilect® (rasagiline mesylate) 1 mg for slowing clinical progression of idiopathic Parkinson's disease. **A**zilect® (rasagiline[a] mesylate; laboratory code TVP-1012) belongs to the pharmacotherapeutic group of anti-Parkinson's disease (PD) drugs, monoamine oxidase (MAO) B inhibitors. Rasagiline [N-propargyl-(1R)-aminoindan] at the therapeutic doses of 0.5 or 1 mg daily, is a potent, site-directed and selective irreversible inhibitor of MAO-B, and can be used in PD as monotherapy or as an adjunct to levodopa (LD) therapy at the therapeutic doses of 0.5 or 1 mg daily.

Figure 1 shows the molecular structural diagram for rasagiline. Rasagiline mesylate is designated chemically as: 1H-Inden-1-amine, 2, 3 dihydro-N-2-propynyl-, (1R)-, methanesulfonate. The empirical formula of rasagiline mesylate is $(C_{12}H_{13}N)CH_4SO_3$, and its molecular weight is 267.34.

Figure 1. Schematic Diagram of Rasagiline Mesylate



Azilect® 1 mg is indicated worldwide for treatment of signs and symptoms of idiopathic Parkinson's disease and was first approved in Israel in January 2005. The Food and Drug

a Azilect® and rasagiline are used interchangeably throughout the document

Administration (FDA) approved rasagiline in May 2006 at a recommended dose of 1 mg once-daily (od) for initial monotherapy, and at doses of 0.5 mg up to 1 mg od (based on clinical response) for adjunctive therapy. Effectiveness was established in three 18- to 26-week, randomized, double-blind, placebo-controlled (PC) trials. In one of these trials, rasagiline was given as initial monotherapy (TEMPO: "**T**VP-1012 in **E**arly **M**onotherapy for **P**D **O**utpatients") in early PD patients not receiving any concomitant dopaminergic therapy, and in the other two (PRESTO and LARGO) as adjunctive therapy to levodopa[1].

TEMPO was carried out as a two period delayed start study. The TEMPO 6-month data, upon which the approval of Azilect® as a symptomatic anti-PD agent was based, were included in the rasagiline New Drug Application (NDA) 21-641. Results from the 12-month TEMPO study indicated that rasagiline's activity may extend beyond a symptomatic effect and were consistent with slowing of clinical progression, but these analyses were not the primary objective of the study. ADAGIO ("**A**ttenuation of **D**isease Progression with **AGI**LECT /AZILECT® **O**nce-daily") was subsequently conducted as a confirmatory pivotal study to demonstrate that rasagiline can modify the clinical progression of PD.

The objective of this document is to describe the clinical evidence of effectiveness that supports the effect of Azilect® on patients with idiopathic Parkinson's disease in slowing clinical progression. The evidence presented consists of two double-blind, randomized, delayed-start studies with placebo-controlled and active-treatment phases – TEMPO and ADAGIO – and supports the basis of independent substantiation of findings[b].

[b] Independent substantiation – "… has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study..."[2]

2.2 Clinical Pharmacology

Rasagiline is rapidly absorbed, reaching the maximum concentration in the bloodstream (C_{max}) in approximately 1 hour. The absolute bioavailability of rasagiline is about 36%. Food does not affect the time to maximum concentration (T_{max}) of rasagiline, although C_{max} and exposure (area under the curve -AUC) are decreased by approximately 60% and 20%, respectively, when the drug is taken with a high fat meal. Because AUC is not significantly affected, rasagiline can be administered with or without food. The mean volume of distribution at steady-state is 87 L, indicating that the tissue binding of rasagiline is in excess of plasma protein binding. Plasma protein binding ranges from 88-94%.

Rasagiline undergoes an almost complete biotransformation in the liver prior to excretion. The metabolism of rasagiline proceeds through two main pathways: N-dealkylation and/or hydroxylation to yield 1-aminoindan, 3-hydroxy-Npropargyl-1 aminoindan, and 3-hydroxy-1-aminoindan. *In vitro* experiments indicate that both routes of rasagiline metabolism are dependent on the cytochrome P450 (CYP) system, with CYP1A2 being the major isoenzyme involved in rasagiline metabolism. Glucuronide conjugation of rasagiline and its metabolites, with subsequent urinary excretion, is the major elimination pathway. After oral administration of ^{14}C-labeled rasagiline, elimination occurred primarily via urine and secondarily via feces (62% of total dose in urine and 7% of total dose in feces over 7 days), with a total calculated recovery of 84% of the dose over a period of 38 days. Less than 1% of rasagiline was excreted as unchanged drug in urine.

Over the dose range of 1-6 mg, the increase in rasagiline AUC is slightly more than proportional, while the increase in C_{max} is proportional. While the mean steady-state half-life is 3 hours, there is no correlation between the pharmacokinetics and pharmacological effect of rasagiline due to its irreversible inhibition of MAO-B.

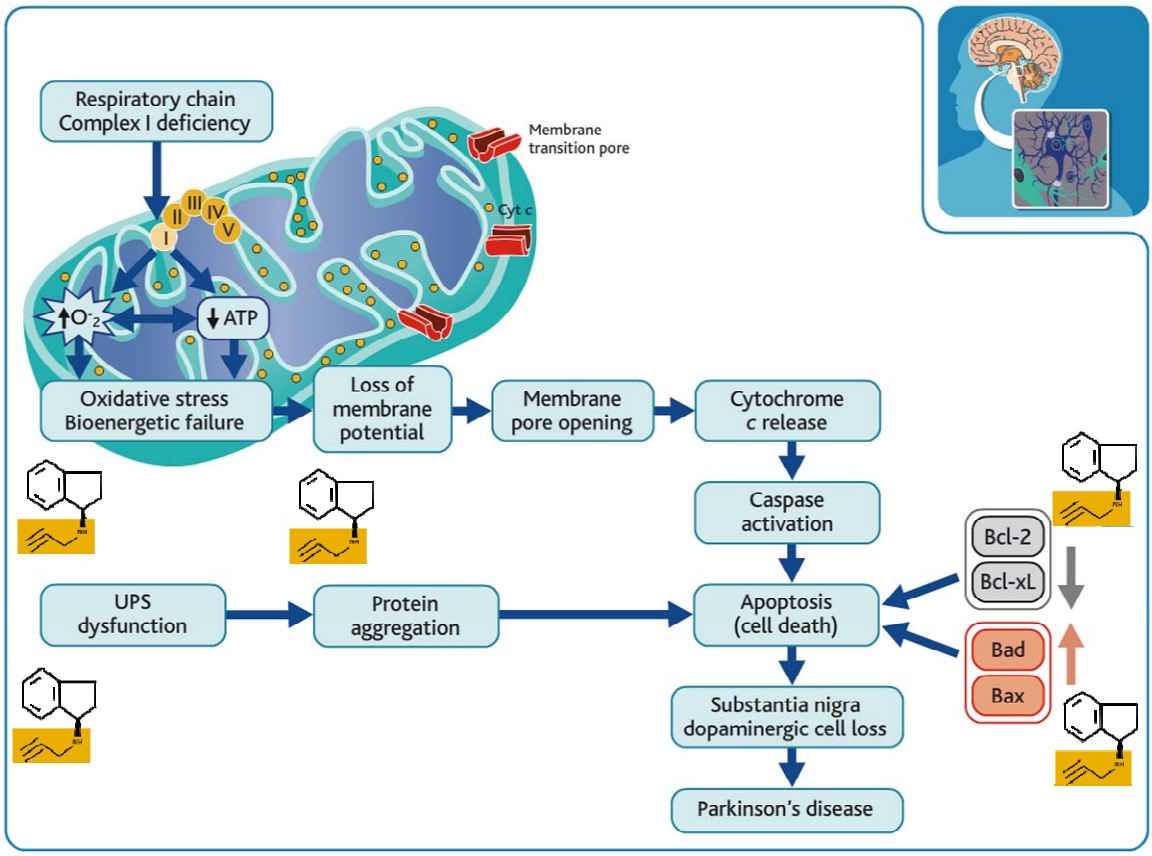
2.3 Potential Basis for Neuroprotective Effects - Rasagiline Effect on Apoptosis

Since cell death is considered to be an important cause in the pathogenesis of PD, drugs that block apoptosis seem to be good candidates to be tested in PD trials[3]. Although the precise mechanisms of action of rasagiline are unknown, its effect on apoptotic pathways, mainly originating from mitochondrial dysfunction, and the consequential neuroprotective activity has been demonstrated *in vitro* and in many animal models. This activity appears to be, at least, partly independent of its MAO inhibitory activity[4-8].

In vitro, rasagiline protects cells from death induced by distinct insults including a variety of neurotoxins such as nitric oxide donor SIN-1, 6-OHDA, MPTP, glutamate, N-methyl (R) salsolinol, alpha-synuclein, and serum and growth factor deprivation[9-13]. It also increases the survival of fetal mesencephalic dopaminergic neurons in culture[14].

Rasagiline prevents the reduction in mitochondrial potential, mitochondrial swelling, and release of cytochrome C, while suppressing the following apoptosis stages: activation of caspases, nuclear translocation of GAPDH, and apoptosis (Figure 2[15]). Rasagiline also increased the levels of anti-apoptotic Bcl-2 and Bcl-xL in SH-SY5Y differentiated cells[5,9,10,12,16-19] and increases glial cell-derived neurotrophic factor (GDNF), a selective survival factor of dopaminergic neurons and less markedly brain-derived neurotrophic factor[19-21].

Figure 2. Mechanism of Antiapoptotic Action of Rasagiline



The neuroprotective activity of rasagiline appears to be independent of MAO-inhibition[5,22]. TVP-1022, the (S)-isomer of rasagiline, which is at least a 100-fold weaker inhibitor of the MAO enzyme, exhibits similar neuroprotective effects (although usually higher doses are required)[7,8,23,24], In addition, the *in vitro* neuroprotective studies carried out with rasagiline were mainly performed in neuronally derived dopaminergic cell lines, which do not contain MAO-B (indeed SH-SY5Y cells only contain MAO-A)[25]. These imply an additional mechanism of action of rasagiline besides MAO-inhibition.

An important component of the actions of rasagiline revolves around the activity of its main metabolite, 1-amino-indan (AI)[26]. In a cytotoxic human neuroblastoma SK-N-SH cell model of high-density culture-induced neuronal death, AI significantly reduces the phosphorylation level of the apoptotic-associated γH2A.X (Ser139) protein, decreases the levels of cleaved caspases-3 and -9, while increasing the levels of phosphorylated PKC as well as Bcl-2 and Bcl-xL[27.] In the same series of experiments, AI was also shown to protect rat pheochromacytoma PC-12 cells against 6-hydroxydopamine neurotoxicity. This leads to the conclusion that aminoindan may contribute to the overall neuroprotective activity of rasagiline[27].

In addition the effect of 1-(R)-aminoindan was tested in two rat models of PD, the 6-hydroxydopamine- and lactacystin[28.] 1-(R)-aminoindan reverses behavioral asymmetry and restores striatal catecholamine levels in these two rat models and significantly protects neurons from hydrogen peroxide-induced oxidative stress.

In vivo, rasagiline reduces neuronal loss in animal models such as of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice[29], oxidative stress[30], hypoxic injury[31], permanent MCA occlusion[32], cerebral trauma[33], amyotrophic lateral sclerosis[34,] transgenic mouse model of multiple system atrophy[35], thiamine-deficient rats[36], and 6-OH dopamine (a rat model for PD)[37]. Rasagiline has a neuroprotective effect in another rat model for PD that used microinjections of lactacystin (an ubiquitin proteosome system inhibitor)[38].

The increased neuronal survival induced by rasagiline in these models was accompanied by improvement of motor function, cognitive state, behavior, and, in some of the models, with increased animal survival.

Taken together, these findings indicate that rasagiline has neuroprotective activity against various insults and toxins in both *in vitro* and *in vivo* models. The protective activity of rasagiline appears to be, at least, partially independent of its MAO inhibitory activity, and may be mediated by other mechanisms. The neuroprotective activity of rasagiline may contribute to its effect on disease progression.

3.0 Parkinson's Disease, a Neurodegenerative Disorder

3.1 Unmet Need for a Drug Affecting the Course of Parkinson's Disease

Diagnosis of PD is based on clinical findings that primarily reflect motor impairment. Early PD is characterized by tremor, muscular rigidity, and bradykinesia, followed later by postural instability[39,40]. By the time motor symptoms become apparent, marked neurodegeneration has already occurred, with the loss of over 70-80% of nigrostriatal dopaminergic neurons[41]. Later symptoms include falls, cognitive and speech impairment, hallucinations, and choking[42]. Severe disability or death may be expected in 25% of the patients within 5 years, and in 80% of the patients within 15 years of onset[42]. Irrespective of age of onset, PD has a major impact on patients, their caregivers, and society in general[43].

Idiopathic PD has an annual incidence in developed countries of 12-20 cases per 100,000 population[44] and is second only to Alzheimer's disease (AD) as the most common neurodegenerative disorder. The onset of PD is insidious and age is the major risk factor[45], with the incidence increasing markedly in the sixth decade[46].

Currently available treatments are primarily based upon replacement of dopamine activity and provide symptomatic control for most PD patients in the early to intermediate phases of their disease when motor impairments predominate[47]. Levodopa, a dopamine precursor, continues to be the gold standard of symptomatic efficacy and is ultimately required by most patients[42,48]. Other drug categories, including dopamine agonists, MAO-B inhibitors, catecholamine-o-methyl transferase (COMT) inhibitors, anticholinergics and glutamate modulators, may represent an alternative, or more often an adjunctive treatment to levodopa. Treatment challenges emerge when PD patients develop non-motor impairments, together with postural instability and gait difficulties, which are unresponsive to dopaminergic treatments[47]. This type of multifaceted disease progression in PD reflects the underlying multisystem neuronal degeneration of PD that characterizes the natural history of the disease. The search for disease-modifying interventions that alter a predictably progressive course remains at the forefront of current PD research.

As reflected by the absence of an FDA approved treatment to slow progression of PD, there is significant challenge in developing pharmacotherapy to slow the course of neurodegeneration. The absence of effective therapy represents a substantial unmet medical need[3].

3.2 Measuring A Drug Affecting the Course of Parkinson's Disease

During the past 20 years, numerous clinical trials attempted to investigate effect on PD progression of various compounds including studies of antiapoptotic agents (riluzole, TCH346, and CEP-1347), antioxidants and mitochondrial stabilizers (Coenzyme Q10 [CoQ10], creatine), dopamine agonists (pramipexole, ropinirole), levodopa, neuroimmunophilin ligands (GPI-1485), neurotrophic factors, and MAO-B inhibitors (selegiline and lazabemide). Until now, none of these drugs succeeded in demonstrating a conclusive effect on disease modification in the clinic[49,50]. Several different trial designs were used to evaluate the above mentioned drugs ability to influence PD progression. However, each design is not without limitations which may have contributed to the disappointing results observed so far.

Many endpoints have been used but fail to delineate the difference between symptomatic effects and slowing of clinical progression of a putative disease modifying agent. An example of a study aiming to assess neuroprotection using the 'time to endpoint' design, is the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study[51]. This placebo-controlled study examined the effects of selegiline and tocopherol (the biologically active antioxidant in vitamin E) on disease progression in 800 early PD patients. The study 'endpoint' was time to initiation of levodopa therapy[51]. The early use of clinical measures such as, time until dopaminergic therapy or change in clinical rating scales as primary outcomes (as used in futility studies), were complicated by confounding effects of symptomatic improvement[52], and a conclusion of disease modification could not be drawn.

The wash-out study design was developed with the aim of eliminating confounding symptomatic effects on the basis that if the effect of a drug is purely symptomatic, any beneficial gain (or decreased extent of loss) would be expected to dissipate on withdrawal[53]. An example of a wash-

out design is the ELLDOPA study, in which the effect of levodopa on the rate of progression of PD was investigated in a randomised, double-blind, placebo-controlled trial[54].

In ELLDOPA, patients were assigned to receive carbidopa–levodopa at several daily doses per group, or a matching placebo, for a period of 40 weeks, after which point patients were to undergo withdrawal of treatment for 2 weeks. The primary outcome was a change in the UPDRS-Total scores between baseline and 42 weeks.

The clinical data suggested that levodopa either slows the progression of PD or has a prolonged effect on the symptoms of the disease. However, the 2-week wash-out period from levodopa may have been insufficient to eliminate fully the effect of the medication on symptoms. Therefore, the observed results may be related to a profound effect of levodopa on symptoms that persists for a long time after the drug has been withdrawn[54].

As such, it is hard to determine the ideal length of the wash-out period, and there are also ethical issues[55]. Short wash-out periods may result in nonsufficient removal of the drug, and the presence of residual effects may mask the study outcome.

Neuroimaging studies have also been employed in bids to overcome the confounding effects of symptomatic benefit[52]. Examples of a neuroimaging studies are the CALM-PD (pramipexole[56]) and REAL-PET (ropinirole[57]) studies which compared the rates of dopamine neurone degeneration by means of dopamine transporter imaging using single-photon emission computed tomography (SPECT) or positron emission tomography (PET).

However, in these studies the results of the radiotracer imaging did not consistently correlate with clinical endpoints Therefore, the technique could not be established as an appropriate surrogate of neurodegeneration in neuroprotection trials for PD[52].

3.2.1 Pathogenic Mechanism of PD

Some of the difficulty in developing effective treatments that slow progression may reflect the absence of clinical surrogate markers that measure disease progression. Although the pathogenic mechanism of PD is not fully understood, PD is well defined by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) in association with intracytoplasmic protein inclusions (Lewy bodies)[58,59]. Lewy bodies are composed principally of highly aggregated alpha-synuclein[60]. Lewy bodies/Lewy neurites are found widely throughout the nervous system in patients with PD[61,62]. There are no biomarkers that measure neuronal dopaminergic cells, discrete cell function or Lewy bodies.

Alternations in the structure of dopaminergic nerve terminals that explain loss of cellular viability because of impaired protein folding or turnover can explain worsening of Parkinsonism without necessarily involving additional neuronal death[63]. In addition, mitochondrial dysfunction, oxidative stress, excitotoxicity, dysfunction of the ubiquitin-proteosome pathway, perturbed calcium homeostasis, and inflammation has been implicated in the process leading to neuronal death[9,16]. These processes coupled with gradual loss of compensatory response in remaining neurons that initially were able to increase dopaminergic input may help to explain some degree of disease progression. Data also suggest that signal mediated apoptosis may cause neuronal cell death[16]. Unfortunately, there are no biomarkers that conclusively measure the effect of these processes on PD.

3.2.2 Clinical Outcomes

Clinical trials that seek to evaluate the impact of pharmacological treatment on disease progression in PD must use clinical outcome measures, all of which pose challenges in interpretation when treatment also produces a symptomatic benefit. These outcome measures could include disability outcomes scales, activities of daily living, slowing the normal progressive increase in symptoms, reducing the need for pharmacological treatment or reduction in the rate of progression in symptoms[63].

Table 1 lists some of the endpoints used in previous clinical trials of disease modification including clinical rating scales, time to specific clinical endpoints, washout studies, and radioligand binding in neuroimaging studies[49,50,52]. Unfortunately, all available endpoints have limitations when trying to assess the impact of pharmacologic treatment on the progression of PD.

Table 1. Endpoints Used in Previous Clinical Trials to Investigate Neuroprotection in Parkinson's Disease

Endpoint	Limitations
Time to milestone of disease progression (e.g., dementia, psychosis, gait impairment)	Natural history is poorly understood and standardized definitions are lacking; late appearance necessitates very long follow-up or recruitment of advanced patients that may not benefit from neuroprotective effects
Washout studies	Length of withdrawal is not defined and residual effect may confound interpretation of results and patient discontinuation during the withdrawal phase
Change in UPDRS scores from baseline	Symptomatic effects confound interpretation
Neuro-imaging biomarkers of dopaminergic function	Interpretation uncertain; cannot exclude the possibility that treatment has a pharmacologic effect on DAT binding (i.e., reduces DAT activity), which could explain decreased ß-CIT midbrain uptake

DAT = striatal dopamine transporter, UPDRS = Unified Parkinson's Disease Rating Scale.

Unified Parkinson's Disease Rating Scale (UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS)[64] is the established scale used in clinical trials to monitor PD symptoms and the inherent progression of symptoms (Appendix A). Total

UPDRS score was defined as the sum of parts I, II, and III (Appendix A). Part I assesses the mental state of the patient in the week prior to the visit, Part II assesses the activities of daily living (ADL) of a patient in the week prior to the visit, and Part III assesses motor disabilities of a patient at the time of the visit. Part I is composed of 4 items, Part II is composed of 13 items, and Part III is composed of 27 items. Overall, the UPDRS is composed of 44 items; each with a possible score ranging from 0 to 4, where 0 represents the absence of impairment and 4 represents the highest degree of impairment. Half point scores were permitted for Part III. The total UPDRS score ranges from 0 to 176 points. Mild patients usually score ~20-30. In early, untreated PD, the annual rate of change is generally about 8-11 units in total UPDRS score[50,65].

3.2.3 Measuring Disease Modification in Drugs with Symptomatic Activity

The goal of therapeutic interventions targeted at disease modification of a progressive disease is to prevent or delay disability, morbidity, and mortality. Disease modification therapies may also lead to immediate symptomatic improvement.

In rheumatoid arthritis, disease-modifying treatment has been available for many years. Such treatment reduces symptoms as well as destruction of joints, leading to reduced disability. Standard markers of joint structure and function are available to affirm an impact on disease progression. Hence, standard parallel design studies can be used to affirm the influence of an intervention on disease progression in rheumatoid arthritis.

In both AD and PD, efforts to confirm an impact on the disease progress have focused on study design methodology that can separate symptomatic benefit from disease modification[65.] Symptom scores in AD and PD form the basis for approval of symptomatic agents.

Many therapeutic agents that are hypothesized to be disease modifying in AD or PD also offer symptomatic benefit. Since there are no efficacy endpoints or biomarkers in either AD or PD that assess the underlying disease progress, disease modification study designs must use standard

symptom scores to assess both types of benefits. Moreover, a special-design is needed to separate out the symptomatic effects from the disease modifying effects[53,66,67,68] .

Both randomized-withdrawal and delayed-start designs[69] have been used in studies of AD and PD to separate symptomatic from disease-modifying effects.

Randomized Washout: A randomized-withdrawal design randomizes both placebo and active-treatment patients to withdrawal after a prolonged period of treatment. Disease symptom scores are followed longitudinally, with a comparison made at the end of the withdrawal period. If a benefit is seen in the active arm and persists after the washout, this is suggestive of a long-lasting effect or DM response. The withdrawal design is complicated by various challenges such as uncertainty of the duration of the withdrawal phase and higher likelihood of patient discontinuation during the withdrawal phase.

Randomized/Delayed –Start Design: to overcome some of these concerns, an alternate design known as a randomized-start design or delayed-start design[53,66,67,70], has been proposed. Patients are randomized to initiate treatment with the study drug or placebo for a fixed time interval. The duration of the PC phase is selected to provide sufficient time for the effects of the treatment on disease symptoms to be stably manifested. At the end of this phase, patients who were randomized to placebo are switched to active treatment and both groups are followed for another fixed time interval to let the symptomatic effects equilibrate. This phase is referred to as the active-control phase. Differences between the two groups at the end of the first (PC) phase could be due to symptomatic and/or disease modifying effects. However, if this difference disappears at the end of second phase, it indicates a sole symptomatic effect. Conversely, if the difference is sustained to some extent and the delayed-start group does not "catch up" with the early-start group, this means that early treatment conferred a benefit that cannot simply be explained by a symptomatic effect alone[65], consistent with the compound having an effect on clinical progression.

Thus, to provide evidence of slowing of disease progression, it is essential to demonstrate that a gap exists between the two groups (placebo and treatment) at the end of the PC phase, and that

this gap is sustained over an extended period of time (early-treatment vs. delayed-treatment) with no evidence that the two groups are coming together during the active-treatment phase, as might occur with a delayed symptomatic effect.

4.0 TEMPO and ADAGIO Study Design: Regulatory History

Given the inherent challenges associated with elucidating drug disease modifying effects in PD (i.e., no established clinical biomarker), there has been an ongoing dialogue between FDA and the pharmaceutical industry on endpoints and analyses to use in clinical trials. To date, consensus remains the goal although two recent important events have helped advance the field closer to understanding the standards that should be applied to drug development for demonstrating disease-modifying effects using the delayed-start design in PD. Those two events are, the 2008 American Association of Pharmaceutical Scientists public meeting of FDA and industry experts in PD, drug development, quantitative clinical pharmacology, and statistics as well as the publication by FDA's Bhattaram et al in 2009.

In the absence of established scientific consensus, TEVA (together with the Parkinson's Study Group), were pioneers and designed and executed the first work (TEMPO) in PD using the delayed-start trial design. TEVA's second trial, ADAGIO, as well as TEMPO were designed in accordance with applicable US FDA and International Conference on Harmonization (ICH) regulatory guidelines. Further, TEVA also sought guidance from the FDA at key milestones during the development process as detailed below.

Given the encouraging findings of the TEMPO study, TEVA sought FDA's advice concerning the kind and scope of additional evidence that would be required to obtain approval of labeling for Azilect that would describe its disease-delaying or disease-modifying effect.

In a meeting on April 15, 2004, the delayed-start design and the use of total UPDRS as a measure for clinical progression was agreed by the FDA as appropriate for the ADAGIO trial. In addition, the Agency suggested inclusion of the non-inferiority slope analysis during the active-treatment phase as a primary endpoint. The issue was further discussed with FDA on December 22, 2004.

The initial study protocol, based on the above discussions, was submitted to the FDA in April 2005. Teva also requested comment and agreement of the protocol by initiating the Special

Protocol Assessment (SPA) process in April 2005 (formal SPA agreement never reached). The Agency provided clinical and statistical comments to Teva in June and July 2005 respectively; a formal letter containing these comments was received in December 2005. An amended protocol was submitted by Teva in November 2006 which related to the Agency's comments. That submission also provided a response to each of the clinical points, and several of the statistical points, raised by the Agency. Among other changes, the amended protocol incorporated FDA's request to define the duration of the early symptomatic phase as 12 weeks (weeks 36-48 in the active-treatment phase; originally, this was defined as 6 weeks).

Statistical issues were further addressed in the Statistical Analysis Plan (SAP) submitted to the FDA in March 2007. Teva understood these to be the Agency's thinking at the time regarding the best statistical approach to be applied to the analysis model:

- Superiority in adjusted mean changes from baseline in UPDRS across Weeks 48-72 (active-treatment phase).
- Non-inferiority of slopes analysis during the active-treatment phase;

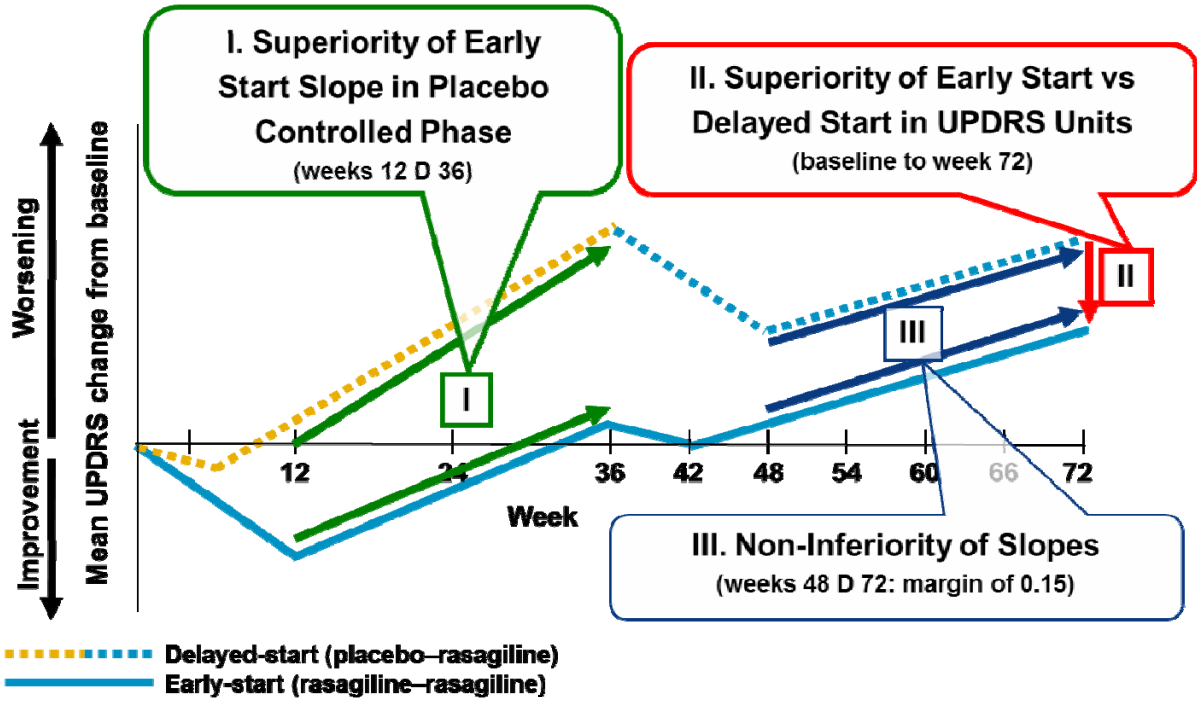
A formal letter from the Agency was received on October 2007 that provided "clinical comments" responses and proposed an alternative SAP. FDA indicated that the suggested SAP reflects "…the Agency's current thinking about a disease modification claim for Parkinson's disease."

The final FDA proposed primary analysis for ADAGIO included three, rather than two, primary outcomes and amended the now second outcome to contain only one timepoint. The additional outcome involved a comparison of slopes during the PC phase of the study (Hypothesis #1 below). FDA recommended that the primary analysis of ADAGIO be based on three hierarchical statistical hypotheses, all involving the UPDRS rating scale.

1. Superiority of the slope of rasagiline over placebo in Weeks 12-36;
2. Superiority of early over delayed start groups at Week 72;

3. Non-inferiority of the slope of early start over delayed start in the active-treatment phase.

Figure 3. Three Pre-specified Hypotheses to Confirm an Effect on the Progression of Parkinson's Disease in a Delayed-Start Design



Adapted from Olanow et al. NEJM 2009[70]

Additional discussion between Teva and the Agency on specific statistical aspects continued during January 2008. The final revised SAP was sent to the Agency by Teva in March 2008 and was in accordance with the FDA's recommendations. It is important to note that the number of patients admitted to ADAGIO was, based on Teva originally proposed analysis plan, sufficient to provide 87% power to compare the adjusted mean changes from baseline in Total UPDRS across weeks 48-72 (active-treatment phase). The power to detect a difference between baseline and Week 72 UPDRS change scores fell to 72% according to FDA requested analysis "change of UPDRS from baseline to Week 72". Unfortunately, at the time these new FDA recommendations were received 11 months had elapsed after the last patient had been enrolled in ADAGIO.

Accordingly, there was no practical way to enroll additional patients to restore ADAGIO's power to the level initially intended.

In a meeting held with the agency in January 2010, Teva indicated its plan to submit a supplemental NDA for a claim that 1 mg rasagiline slows the clinical progression of Parkinson's disease. FDA expressed the view that with the currently available results from ADAGIO and TEMPO the data was not sufficient to conclude that there is support for a claim of slowing of disease progression for rasagiline. However, Teva proposed to advance with submitting an sNDA in any event, indicating that they would provide additional analyses to support a signal of effect that could not be explained by symptomatic effects alone and that the benefits observed indicated that the rasagiline slowed clinical progression of the disease. FDA expressed their agreement that an NDA supplement for a disease modification claim supported by the TEMPO and ADAGIO trial results could be filed. The Agency encouraged Teva to initiate a new clinical trial to support replication of effect for the 1 mg dose. The Agency further noted that the sponsor could both submit an sNDA and initiate another clinical trial.

Additionally, FDA commented that it desired certain safety analyses in a supplemental NDA for this claim for data from TEMPO and ADAGIO separately and also for pooled analyses for both studies. An Advise/Information Request (AIR) was received by Teva on April 2010 detailing the additional safety analyses that would be necessary for a sNDA. These were submitted within the sNDA on Dec. 23, 2010.

A summary of regulatory milestones for the rasagiline disease modification program is presented in Table 2.

Table 2. Regulatory Milestones for Rasagiline Disease Modification Program

Date	Milestone
July 2003	TEMPO completed; TEMPO showed that patients who started rasagiline earlier (early-start group) had less deterioration in total UPDRS scores than did patients for whom initiation of treatment was delayed by 6 months, suggesting an effect of rasagiline on clinical progression of PD.
15 April 2004	Meeting with FDA to discuss design of additional trial for measuring clinical progression using the delayed-start design employing UPDRS (ADAGIO study). In addition, the FDA suggested inclusion of the non-inferiority slope analysis during the active-treatment phase as a primary endpoint
22 December 2004	Teleconference with FDA to discuss the design and analysis issues
11 April 2005	ADAGIO protocol submitted to FDA
04 November 2005	ADAGIO-first patient in
09 December 2005	FDA provided official clinical and statistical comments on ADAGIO to Teva
May 2006	NDA 21-641 for symptomatic treatment of PD approved by FDA
07 November 2006	Teva submitted an amended ADAGIO protocol, which incorporated FDA's request to define the duration of the early symptomatic phase as 12 weeks – Weeks 0-12 in the PC phase and Weeks 36-48 in the active-treatment phase (originally defined as 6 weeks).
8 March 2007	SAP submitted to FDA included the two primary analyses - Teva understood these to be the Agency's thinking at the time regarding the best statistical approach to be applied to the analysis model: • Non-inferiority of slopes analysis during the active-treatment phase; • Superiority in average change from baseline to active-treatment phase in UPDRS Weeks 48-72.
22 October 2007	Agency proposed an alternative SAP on October, 2007 indicating that the suggested SAP reflects "…the Agency's current thinking about a disease modification claim for Parkinson's disease." The FDA SAP proposed three primary outcomes, including an additional primary analysis . The new proposed principal efficacy analysis consisted of three hierarchical statistical hypotheses to be applied on the primary efficacy endpoint: To note that these changes were requests eleven months after the last patient enrolled in ADAGIO. 1. Superiority of the slope of rasagiline over placebo in Weeks 12-36 2. Superiority of early over delayed start (DS) groups at Week 72 3. Non-inferiority of the slope of early start (ES) over delayed start in the active-treatment phase
04 March 2008	In accordance with FDA's requests Teva submitted final, revised SAP that consisted of the 3 hierarchical statistical hypotheses To note that the sample size in the study provided 87% power according to the original change the superiority test (Hypothesis #2) average of Weeks 48-72, and only 72% according to the Week 72

	endpoint requested by the FDA The FDA request to change the SAP was made eleven months after the last patient enrolled in ADAGIO and enrollment had been closed.
28 January 2010	Type C meeting conducted with FDA. FDA expressed their view that with the currently available results from ADAGIO and TEMPO it is difficult to conclude that there is support for a slowing of clinical progression claim and encouraged initiation of a new clinical trial, due to inconsistency of results between 1 and 2 mg. Should Teva submit a supplemental New Drug Application (sNDA), FDA requested safety data analyses by study (TEMPO and ADAGIO separately) and for pooled data (requests detailed in an Advise/Information Request [AIR] from FDA dated 14 April 2010).
23 December 2010	Teva filed a slowing clinical progression sNDA for rasagiline 1 mg.

5.0 Clinical and Statistical Methodology in TEMPO and ADAGIO

The TEMPO study was conducted by the Parkinson Study Group (PSG), an independent group of physicians and health care providers from medical centers in the United States and Canada, using their Clinical Trials Coordination Center and Steering Committee.

TEMPO randomized patients to 3 treatment groups: rasagiline 1 mg for 52 weeks, placebo for 26 weeks followed by rasagiline 2 mg for 26 weeks, or rasagiline 2 mg for 52 weeks. The 52-week TEMPO analysis compared the UPDRS score at week 52 between the early- and delayed-start groups[71, 72].

A Clinical Oversight Committee comprised of leading PD experts was responsible for the design of the ADAGIO study protocol and analysis plan, and the interpretation of study results upon the completion of the study. The study population, study design, efficacy rating scales and measurements, and time points used for evaluations in the ADAGIO study were consistent with the approaches advised by the FDA for evaluating the effect of treatment on clinical progression of PD.

They contributed largely to the design of the protocol and analysis of data. In the ADAGIO study, PD patients were randomized to 4 treatment groups: rasagiline 1 mg for 72 weeks, rasagiline 2 mg for 72 weeks (early-start groups), placebo for 36 weeks followed by rasagiline 1 mg for 36 weeks or placebo for 36 weeks followed by rasagiline 2 mg for 36 weeks (delayed-start groups). Thus there were two phases in the study: a PC phase and an active treatment phase.

5.1 Study Design and Objectives

5.1.1 TEMPO

Study design: TEMPO was a multicenter, double-blind, PC, parallel group, phase III clinical study to assess the efficacy, tolerability, and safety of 1 and 2 mg doses of rasagiline in early-stage PD patients not treated with levodopa. The PC phase of TEMPO was a 26-week double-blind, PC phase while the active-treatment phase was a 26-week double-blind, active-treatment phase

Eligible patients were randomized in a 1:1:1 ratio into one of the following three treatment groups:

- 1 mg/day rasagiline during the PC phase and the active-treatment phase (1 mg early start)
- 2 mg/day rasagiline during the PC phase and the active-treatment phase (2 mg early start)

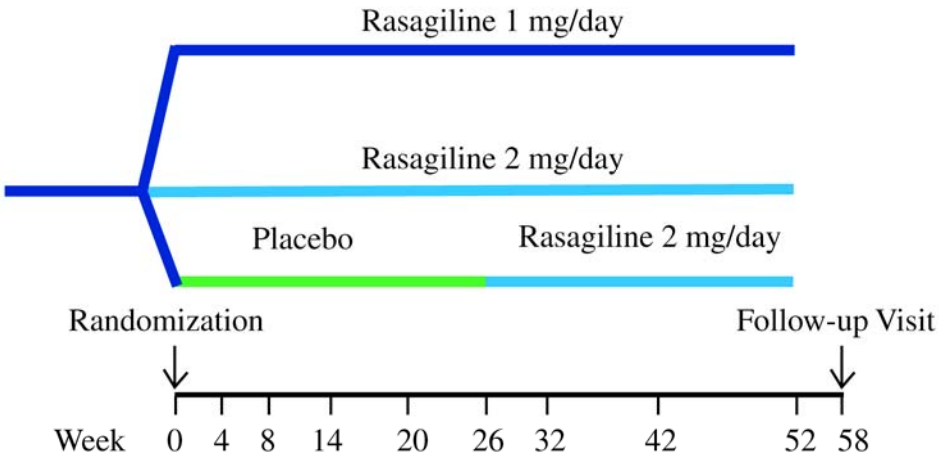
- placebo during the PC phase followed by 2 mg/day rasagiline during the active-treatment phase (2 mg delayed start)

There was no delayed-start group for the 1 mg dose in the TEMPO study

During the PC phase (PC Phase), patients who required additional PD therapy were withdrawn from this Phase, and were allowed to begin active treatment with rasagiline in the active-treatment phase. For these patients, levodopa (or other anti-PD therapy) was initiated if the patients still required additional therapy after 2 or more weeks on rasagiline. Scheduled in-clinic visits were conducted at baseline and at weeks 4, 8, 14, 20, and 26.

In the active-treatment phase, patients who received rasagiline 1 mg during the PC phase continued to receive 1 mg during the active-treatment phase and patients who received rasagiline 2 mg during the PC phase continued to receive 2 mg. Patients who received placebo during the PC phase received rasagiline, beginning at 1 mg/day for the first week and increasing to 2 mg/day for the remaining 25 weeks of the active-treatment phase. If the investigator determined that a patient needed additional anti-PD therapy after completing the PC phase and at least 2 weeks of the active-treatment phase, levodopa or a dopamine agonist could be added to study drug. The efficacy analysis did not include UPDRS measurements for patients on these medications. Scheduled in-clinic visits were conducted at Weeks 32, 42, and 52. A termination visit occurred at Week 58. Following a protocol amendment in Canada, an additional 2 visits were added at Weeks 29 and 37. The study design and visits schedule are presented in Figure 4.

Figure 4. TEMPO Study Design



Major inclusion & exclusion criteria: Male or female (not pregnant) patients age 35 years or older with early idiopathic PD and Hoehn and Yahr (H&Y) stage ≤3 (<3 in Canada), confirmed at screening by the presence of at least two of the cardinal signs (resting tremor, bradykinesia, rigidity) without any other known or suspected cause of parkinsonism (if tremor was not present, with unilateral onset and persistent asymmetry), not requiring anti-PD therapy at enrollment. Concomitant anticholinergic medication was permitted.

Study Objectives: The objectives of the TEMPO study were to assess the efficacy, tolerability, and safety of rasagiline 1 and 2 mg in early PD patients who were not receiving or did not require levodopa/carbidopa therapy. The primary endpoint was a comparison of UPDRS scores at 26 weeks.

An additional prespecified exploratory analysis, based on the entire 52-Week study period, compared the change in UPDRS from baseline to week 52 in patients assigned to early treatment with those assigned to a delay in treatment. Since there was no 1 mg delayed-start group, both the 1 mg and 2 mg early-start groups were compared to the 2 mg delayed-start group.

5.1.2 ADAGIO

Study design: ADAGIO was a multicenter, double-blind, delayed-start, PC, parallel-group Phase IIIb study that was conducted to assess the potential of rasagiline as a disease-modifying therapy in early untreated idiopathic PD patients. The study was completed in April 2008.

Figure 5 shows the two-phase study design and visit schedule. The placebo-controlled phase consisted of 36-weeks of double-blind treatment including a placebo arm, and the active-treatment phase consisted of 36-weeks of double-blind active treatment.

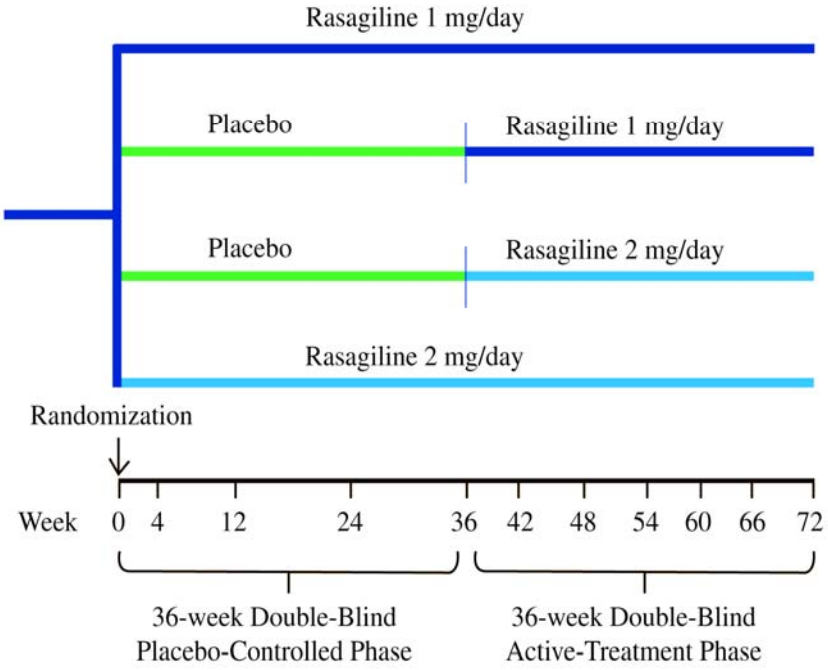
Eligible patients were randomized in a 1:1:1:1 ratio into one of the following four treatment groups:

- 1 mg/day rasagiline during the PC phase and the active-treatment phase ("1 mg early start")
- 2 mg/day rasagiline during the PC phase and the active-treatment phase ("2 mg early start")
- Placebo during the PC phase followed by 1 mg/day rasagiline during the active-treatment phase ("1 mg delayed start")
- Placebo during the PC phase followed by 2 mg/day rasagiline during the active-treatment phase ("2 mg delayed start")

If, at any time during the PC phase, the investigator determined that a patient needed additional anti-PD therapy (based on accumulating disability in the patient's functioning, independence, occupation, and balance), the patient proceeded to the active-treatment phase of the study. Scheduled in-clinic visits were conducted at baseline and at Weeks 4, 12, 24, and 36.

In the active-treatment phase (double-blind active treatment), patients who received rasagiline 1 mg during the PC phase continued to receive 1 mg during the active-treatment phase and patients who received rasagiline 2 mg during the PC phase continued to receive 2 mg during the active-treatment phase. Patients who received placebo during the PC phase received rasagiline 1 mg or 2 mg during the active-treatment phase based upon their initial randomized assignment. If, at any time during the active-treatment phase, the investigator determined that a patient needed additional anti-PD therapy, the patient was prematurely withdrawn from the study. Scheduled in-clinic visits were conducted at Weeks 42, 48, 54, 60, 66, and 72. The study design and visits schedule are presented in Figure 5.

Figure 5. ADAGIO Study Design



Major inclusion & exclusion criteria: Male or female (not pregnant) patients age 30-80 years with early (<1.5 years from time of documented diagnosis) idiopathic PD and H&Y stage <3, confirmed at screening by the presence of at least two of the cardinal signs without any other known or suspected cause of parkinsonism (if tremor was not present, with unilateral onset and persistent asymmetry), not requiring anti-PD therapy at enrollment, and no expected requirement for the next 9 months (PC phase).

Objectives: The primary objective of the ADAGIO study was to determine whether rasagiline slowed the clinical progression of PD by analyzing the three hypotheses defined in Figure 3. These three hierarchal hypotheses constituted the primary efficacy analysis and were based on changes from baseline in total UPDRS score (Parts I, II, and III).

5.2 Statistical Methodology

5.2.1 TEMPO

The efficacy cohort for the 52-week analysis included all patients with at least one UPDRS measurement in the active-treatment phase, before the onset of additional anti-PD therapy. The 52-week analysis for the TEMPO study was change from baseline in total UPDRS score from baseline to the last observed value (LOV) during the active-treatment phase. ANCOVA was used to compare changes from baseline to the final visit for each early-start group vs. the delayed-start group. Baseline values and treating center were included as covariates. For each variable analyzed, effect size was defined as the difference between adjusted means for each early-start rasagiline group (1 mg or 2 mg) vs. the delayed-start rasagiline group (2 mg).

5.2.2 ADAGIO

5.2.2.1 Analysis Data Sets

Analysis data sets were defined for the efficacy analyses in the ADAGIO study

- Intent-to-Treat Data Analysis Set (ITT) consisted of all patients randomized with at least one post-baseline measurement. In accordance with the ITT principle, patients were kept in their originally assigned treatment group.

For the analysis of Hypothesis #1 of the primary efficacy analysis, the following sub-cohort was defined:

- Modified ITT Data Analysis Set (mITT) consisted of patients who had at least one of the UPDRS assessments performed at Weeks 12, 24, and 36 as mandated in the ADAGIO protocol

For the analyses of hypotheses #2 and #3 the following data analysis set was defined

- Active Efficacy Data Analysis Set (ACTE) consisted of all patients who entered the active-treatment phase of the trial with at least 24 weeks of treatment during the PC

phase of ADAGIO, and at least one available total UPDRS measurement during the active-treatment phase from Week 48 onwards in ADAGIO.

Two additional data analysis sets were defined in ADAGIO for supportive analyses of Hypotheses #1, #2, and #3:

- Completers Data Analysis Set (CO) consisted of all patients who completed at least 34 weeks of treatment in the PC phase, and at least 34 weeks of treatment in the active-treatment phase. The cutoff of 34 weeks rather than 36 weeks was implemented to allow for some flexibility in the scheduling of the Week 36 and Week 72 visits.
- Per Protocol Data Analysis Set (PP) was a subset of the CO data analysis set, excluding patients with the following major protocol violations: use of anti-PD medications during study and overall compliance to study drug < 80%.

5.2.2.2 Multiple Comparisons Adjustment

The Hochberg's Step-Up Bonferroni method[73] for multiple comparisons between treatment groups (2 comparisons: early-start group compared to delayed-start group for rasagiline 1 mg and 2 mg), in combination with the hierarchical method for the 3 hypotheses testing and for the secondary endpoint, were used to maintain the experiment-wise type I error of 5%.

If the first null hypothesis comparing the early-start group to the delayed-start group was rejected for both rasagiline doses at an alpha level of 5% then no adjustment to the alpha level was to be performed and both comparisons were to be declared as statistically significant. If the first null hypothesis was not rejected for one of the doses at an alpha level of 5%, then the other dose was to be tested using an alpha level of 5%/2 = 2.5%.

Each statistically significant dose, as determined by the test of Hypothesis #1, was to be further tested for Hypothesis #2 using an alpha level of 0.05 and the Hochberg's Step-Up Bonferroni method as described for Hypothesis #1 above. The same procedure was to be applied for testing Hypothesis #3 and the secondary endpoint: change in total UPDRS from baseline to LOV in the PC phase

5.2.2.3 Primary Efficacy Analysis

For both early- vs. delayed-start comparisons (1 and 2 mg), three hypotheses were pre-specified for analysis based on changes from baseline in total UPDRS scores (sum of Parts I, II, and III)

Hypothesis #1: Slopes Superiority of Rasagiline over Placebo in the PC Phase (from Week 12 to Week 36)

H_0: Slope $_{(Rasagiline)}$ – Slope$_{(Placebo)}$ = 0

H_A: Slope $_{(Rasagiline)}$ – Slope$_{(Placebo)}$ ≠ 0

where slope was the change from baseline in total UPDRS per week.

All available post-baseline observations in the PC phase of the trial were analyzed (modified ITT data analysis set, Weeks 12, 24, and 36). The placebo groups for rasagiline 1 mg and 2 mg were combined to one placebo group.

The statistical model that gave estimates for the changes from baseline in total UPDRS per week (slope) was a Repeated Measures Mixed Linear Model with random intercept and slope (SAS® MIXED procedure with RANDOM sub-command). The model included the following fixed effects: treatment group, continuous week in trial by treatment interaction, center, and baseline total UPDRS score. The individual patient intercept and the week effects were also included in the model as random effects. An unstructured covariance matrix between the intercept and slopes estimates, was used.

Two comparisons were derived from the model: slope difference of rasagiline 1 mg group from the placebo group and slope difference of rasagiline 2 mg group from the placebo group.

Hypothesis #2: Superiority of Early over Delayed Start of Rasagiline at Week 72

In the original SAP submitted to the FDA in March 2007 (as described in Section 4.0, ADAGIO Study Design - Regulatory history), this hypothesis was analyzed by comparing the adjusted mean changes from baseline in Total UPDRS across Weeks 48-72 (active-treatment phase) using a repeated measures ANCOVA model (SAS® MIXED procedure) with categorical week in trial. It should be noted, that the study was powered per the original SAP according to this analysis and according to Hypothesis #3 (see Section 5.2.2.5).

Following the interactions with the FDA, the analysis was revised in the final SAP to "change of UPDRS from baseline to Week 72", as described in the below test of Hypothesis #2:

H_0: $\mu_{\text{(Early Start Group at Week 72)}} - \mu_{\text{Delayed Start Group at Week 72)}} = 0$

H_A: $\mu_{\text{(Early Start Group at Week 72)}} - \mu_{\text{(Delayed Start Group at Week 72)}} \neq 0$

In the primary analysis of (the revised) Hypothesis #2, observations of patients entering the active-treatment with at least 24 weeks of treatment during the PC phase and at least one available total UPDRS measurement during the active-treatment phase from Weeks 48, 54, 60, 66, or 72 were analyzed (ACTE data analysis set).

The statistical model was a repeated measures model (SAS® MIXED procedure with REPEATED sub-command) that was employed simultaneously for the two contrasts of early vs. delayed start for 1 and 2 mg. The model included the following fixed effects: categorical week in trial by treatment interaction, center, and baseline total UPDRS score. An unstructured covariance matrix for repeated observations within patients was used.

Least Square Means (LSM) at Week 72 of the change from baseline in total UPDRS were compared between the rasagiline 1 mg early-start group and the rasagiline 1 mg delayed-start group and between the rasagiline 2 mg early-start group and the rasagiline 2 mg delayed-start group.

Hypothesis #2 –separate datasets (alternative analyses)

Following the unblinding of ADAGIO, it became apparent that the pattern of response of the two dose levels in the active-treatment phase was different. An underlying assumption for the analyses in the active-treatment phase, based on a combined dataset (which includes all 4 treatment arms), was that the effect of the adjusting covariates in the model (baseline UPDRS and center) is the same for both dose levels (1 mg early & delayed start groups versus 2 mg early & delayed start groups). This means that there is no interaction between dose level and the pre-specified covariates in the model: baseline UPDRS and center. Interactions of dose level by baseline UPDRS and dose level by center means that the baseline UPDRS and center had a different impact on the dependent variable, UPDRS change from baseline (this different impact is fixed across visits), for each dose level (early and/or delayed-start).

These interactions were tested using the model for Hypothesis #2. With the addition of terms for estimating the interaction of dose level (1 mg early & delayed start arms versus 2 mg early &

delayed start arm) by baseline UPDRS and by center, both interactions were found to be important (p=0.0481 for dose level by baseline UPDRS; p=0.0125 for dose level by center).

Estimation of the treatment effect of 1 mg and 2 mg in the presence of the above interactions could be addressed by either addition of interaction terms to the model (as above) or by performing analyses on separate datasets employing the original model structure. The latter option is possible because of the unique design of the ADAGIO study, which includes a separate control for each of the rasagiline doses tested (the delayed start arm). Thus, ADAGIO can be viewed as two studies combined into one.

At the time, the separate datasets option was chosen as the preferred one and the most appropriate way to analyze the data for hypotheses #2 and #3, thus preserving the original model structure that was defined in the SAP.

Hypothesis #3: Non-Inferiority of slopes for Early Start over Delayed Start in the Active-treatment phase

H_0: $\text{Slope}_{(\text{Early Start Group})} - \text{Slope}_{(\text{Delayed Start Group})} > 0.15$

H_A: $\text{Slope}_{(\text{Early Start Group})} - \text{Slope}_{(\text{Delayed Start Group})} \leq 0.15$

where slope was the change from baseline in total UPDRS per week.

Non-inferiority for the difference in slopes between the treatment groups was determined based on a non-inferiority margin of 0.15 UPDRS points per week. One-sided 95% confidence intervals (CI) were calculated for the difference between the slopes of the rasagiline 1 mg early-start group and the rasagiline 1 mg delayed-start group and between the slopes of the rasagiline 2 mg early-start group and the rasagiline 2 mg delayed-start rasagiline group.

In this analysis, observations of all patients entering the active-treatment phase with at least 24 weeks of treatment during the PC Phase and at least one available total UPDRS measurement during the active-treatment phase from Weeks 48, 54, 60, 66, or 72 were analyzed (ACTE data analysis set).

The statistical model was a repeated measures mixed linear model, with random intercept and slope (SAS® MIXED procedure with RANDOM sub-command). The model included the following fixed effects: treatment group, continuous week in trial by treatment interaction, center, and baseline total UPDRS score. Individual patient intercept and the week effects were also included in the model as random effects. An unstructured covariance matrix between the intercept and slopes estimates was used.

Test of Linearity

A linearity test for the active-treatment failed to reject the null hypothesis (p=0.0893), so an alternative model was not applied.

5.2.2.4 Sensitivity Analyses

Multiple statistical analyses evaluated the effect of missing observations on primary analysis findings:

Analyses pre-defined in the SAP for Hypotheses #1, #2 and #3:

1. The primary analyses were performed on the completers and per-protocol analysis sets, defined in Section 5.2.2.1.

2. Multiple imputation method (Rubin[74]; Little and Rubin[75]), using the SAS MI and MIANALYZE procedures was applied to hypotheses #1, #2 and #3 as follows: This analysis assumes that the nature of the missing values mechanism is Missing At Random (MAR). The multiple imputation method is performed in 3 stages:

   - First, the Markov-Chain-Monte-Carlo (MCMC) method is used on the UPDRS repeated measurement at Weeks 0, 12, 24, 36, 42, 48, 54, 60, 66 and 72 to impute the non-monotone missing values and to achieve a monotone missing values structure. The number of imputations used is 5. This procedure is done for each treatment group separately.

   - Second, on the output data from the first stage, the monotone imputation method (with one imputation) is used on the repeated UPDRS measurement at Weeks 0, 12, 24, 36, 42, 48, 54, 60, 66 and 72, subject age, time to additional anti PD treatment need as continuous variables, and on treatment group, center and sex as categorical (class) variables. The regression method is used for the UPDRS measurements.

- Finally the model used for the principal analysis is activated on the imputed data set, separately for each one of the 5 imputation sets, yielding 5 parameter estimates sets that are analyzed in the MIANALYZE procedure for appropriate parameter estimates and p-value calculations.

3. Imputing missing data with means: The mean of the change from baseline of the rasagiline 1 mg/2 mg delayed-start group, at the relevant weeks was used to impute the missing data of all subjects (regardless if assigned to delayed or early start groups), receiving delayed or early rasagiline 1 mg/2 mg.

Post-hoc Analyses for Hypothesis #2:

1. A Repeated Measures Model using all observed data from Week 12 to 72 was performed *post-hoc*. This analysis assumes that the nature of the missing values mechanism is Missing At Random (MAR) (Little and Rubin[75]).

2. The primary model with the addition of dose level (1 mg or 2 mg) by baseline UPDRS interaction and dose level by center interaction.

3. Change in Total UPDRS from baseline to Week 72 using LOCF in the active-treatment phase. ANCOVA was performed separately for each dose level. An additional analysis performed on rank-transformed data was performed as well.

4. Propensity Score Analysis:

   In the article "The delayed-start study design" (D'Agostino, et al.[69]), the author suggests that imbalance of the active period subset of the original randomized groups may be a big problem and that propensity scores may help address analysis validity questions related to such an imbalance. As a post-hoc analysis, requested by the FDA as well, a propensity score adjusted analysis was performed aimed to reduce the possible bias in the treatment effect if such imbalance exists. In this method, differences between the early and delayed groups in the distribution of the various baseline covariates are summarized into one measure, namely the propensity score. The analysis included two stages for each of the doses 1 mg and 2 mg:

   Step 1: Calculation of the propensity score for each patient, namely, an estimation of the probability of belonging to the early-start group (as opposed to the delayed-start group) given a broad set of baseline covariates; The propensity scores were estimated using logistic Regression. The explanatory variables in the model included: age, gender, country, time since diagnosis (months), Modified Hoehn and Yahr score at baseline, Total UPDRS score at baseline, quartile of Total UPDRS

score at baseline (categorical variable), UPDRS motor score and UPDRS ADL score at baseline, Baseline BECK score. Second order interactions were also included.

Step 2: Incorporating the propensity score into the model for testing Hypothesis #2 using two adjusting approaches:

- Including the raw propensity score as a continuous covariate,
- Sub- classifying the range of the raw propensity scores into quintiles and including the quintile as a categorical variable (with 5 levels).

5. Matched Pairs Data Analysis

Additional sensitivity analysis was performed as an attempt to evaluate the possible bias due the fact that Hypothesis #2 was analyzed on a sub-population of the study. This sensitivity analysis aimed also to better balance between the early and delayed groups with respect to baseline UPDRS and subjects who failed to be included in the ACTE data analysis set.

The matched pairs analysis included the following steps:

Step 1: For each dose in the ITT analysis set (1 mg and 2 mg), the delayed and early subjects where matched into pairs according to their relative baseline UPDRS location (rank) within the group.

Step 2: If any one of the subjects with a matched pair was not included in the ACTE data analysis set then both subjects were redacted. We refer to the data as matched pairs data.

Step 3: The original predefined model for Hypothesis #2 was applied to the matched-pairs data.

5.2.2.5 Sample Size and Study Power

The following power considerations were taken for determination of the sample size:

A total of 935 patients entering the active-treatment phase (about 1,100 patients randomized, assuming 15% dropouts), provides:

- 87% power for detection (at 5% significance level) of a difference in the adjusted mean changes from baseline in total UPDRS across Weeks 48-72 (active-treatment phase) between the two treatment groups assuming a true difference of 1.8 UPDRS points. Towards the end of the study conduct (eleven months after the last patient enrolled in ADAGIO), the FDA requested that the superiority test for this hypothesis be based on change from baseline at Week 72, rather than all the values from Weeks 48-72, which resulted in reduction in power to 72%, due to the increased variability of the new endpoint.

- 99% power to demonstrate non-inferiority between the slopes of the rasagiline 1 mg (2 mg) early-start group as compared to rasagiline 1 mg (2 mg) delayed-start group using a 2.5% significance level due to adjustment for multiple comparisons and a non-inferiority threshold of 0.15 UPDRS points per week.

5.2.3 TEMPO Analysis Using ADAGIO Methods

The three hypotheses comprising the primary endpoint as pre-defined for the ADAGIO study were used to analyze TEMPO post-hoc in the same manner as carried out in the ADAGIO study (Section 5.2.2.3), taking into consideration the different duration of study and visits schedule.

Since the visits schedule differed between the two studies, a matching procedure was applied (Table 3) to be used in the definition of data analysis sets.

Table 3. Time Points of UPDRS Measurements in ADAGIO/TEMPO

ADAGIO and TEMPO	Placebo-Controlled Phase							Active-treatment phase					
Visit Week	**0**	**4**	**8**	**12/14***	**20**	**24/26***	**36**	**42/32***	**48**	**54/42***	**60/52***	**66**	**72**
Week in Active-treatment phase								**6**	**12**	**18/16***	**24/26***	**30**	**36**
ADAGIO	+	-	-	+	-	+	+	+	+	+	+	+	+
TEMPO	+	+	+	+	+	+	-	+	-	+	+	-	-

*ADAGIO/TEMPO

Analysis Data Sets

Analysis data sets defined for the efficacy re-analyses of the TEMPO using ADAGIO methodology:

- Intent-to-Treat Data Analysis Set (ITT) consisted of all patients randomized with at least one post-baseline measurement. In accordance with the ITT principle, patients were kept in their originally assigned treatment group.

For the analysis of Hypothesis #1 of the primary efficacy analysis, the following cohort was defined:

- Modified ITT Data Analysis Set consisted of patients who had at least one of the UPDRS assessments performed at Weeks 14, 20 and 26 in TEMPO.

For the analyses of Hypotheses #2 and #3, the following data analysis set was defined:

Active Efficacy Data Analysis Set (ACTE) consisted of all patients who entered the active-treatment phase of the trial with at least 24 weeks of treatment during the PC phase of TEMPO, and at least one available total UPDRS measurement during the active-treatment phase from Week 42 onwards in TEMPO.

The following sensitivity analyses were adapted from ADAGIO, based on the respective visits schedule:

- Analysis of Completers
- Imputing missing data using means of delayed group.

- Multiple imputation method
- Repeated Measures based on observed data in Weeks 14 -52

5.2.4 Natural History Staggered Start Analysis – ADAGIO and TEMPO Studies

Post-hoc, an analytic approach referred to as the Natural History Staggered Start analysis (NHSS) was used to analyze the slope differences between the placebo and treated groups. The methodology was proposed by Suzanne Hendrix (first presented at the 2007 Joint Statistical Meetings) with the aim to take into account that a simple slope separation does not necessarily indicate disease modification. The NHSS approach uses the relationship between the baseline UPDRS scores and the immediate (symptomatic) response in order to try and estimate the change in symptomatic effects with time. The Natural History Estimate (NHE) adjusts the estimated slope difference between the treatment and placebo groups to account for these changing symptomatic effects; therefore, the main reason why simple slope separation does not necessarily indicate disease modification is taken into account.

The NHSS approach assumes that (1) the symptomatic effect is early, and that (2) the symptomatic effects seen at the start of the study are similar to those that affect the patients longitudinally. A detailed description of the assumptions, the statistical model, and the derivation of the NHSS disease modification estimate are provided in Appendix C.

The NHSS model was fit to the data from the ADAGIO and TEMPO studies, and the NHE was calculated by using the estimate of the slope separation and adjusting out the symptomatic changes over time (using Tau). Two models were run for each study, one using first phase data plus extension phase data for the early start group (referred to as model 1) and one using first phase data only (model 2). The models that were run on the ADAGIO and TEMPO data used a linear fit over time for the UPDRS change scores, and also a linear fit for baseline score.

6.0 Efficacy Results in TEMPO and ADAGIO

A total of 404 patients were enrolled and randomized to study drug in the TEMPO study: 138 patients entered the 2 mg delayed-start treatment group (placebo), 134 patients entered the 1 mg early-start treatment group, and 132 patients entered the 2 mg early-start treatment group (Table 7).

A total of 1,176 patients were enrolled and randomized, while a total of 1,174 received at least 1 dose of study drug in the ADAGIO study: 288 patients entered the 1 mg early-start treatment group, 293 patients entered the 2 mg early-start treatment group, 298 patients entered the 1 mg delayed-start treatment group, and 295 patients entered the 2 mg delayed-start treatment group. The 2 additional subjects originally randomized to the 1 mg delayed-start group withdrew consent prior to receiving any study drug (Table 8).

6.1 Demographic and Other Baseline Characteristics

Table 4 shows the demographic characteristics of patients enrolled in TEMPO and ADAGIO. Both studies enrolled more males than females and had similar mean ages. TEMPO was conducted in the US/Canada while ADAGIO was an international study conducted in USA/Canada, Europe, Argentina, and Israel.

Table 4. Demographic Characteristics of Patients by Study – ITT Data Analysis Set

Demographic Characteristic	TEMPO N=404	ADAGIO N=1174[a]
Gender, n (%)		
Female	147 (36.4%)	457 (38.9%)
Male	257 (63.6%)	717 (61.1%)
Age (years)		
Mean (SD)	60.8 (10.8)	62.2 (9.6)
Range	32-92	31-81
Race, n (%)		
Caucasian	383(94.8%)	1147 (97.7%)
Geographical Region, n (%)		
North America (USA/Canada)	404 (100%)	494 (42.1%)
Europe/Argentina/Israel	–	680 (57.9%)

a. Two patients out 1176 randomized withdrew consent prior to receiving any study drug.

Table 5 and Table 6 show PD characteristics by treatment group in TEMPO and ADAGIO, respectively. Within each study, baseline demographic and PD characteristics were comparable among the treatment groups. Patients enrolled in ADAGIO had an earlier stage of PD, as reflected by a shorter time from PD diagnosis at screening, (4.5 months compared to 1 year in ADAGIO and TEMPO, respectively), and lower baseline total UPDRS score (mean = 20.4 vs. mean = 25.0 for the respective studies).

Table 5. TEMPO: Baseline PD Characteristics

TEMPO		**1 mg**	**2 mg**	**Placebo**	**All**
Parkinson Disease Duration (years)	N	134	132	138	404
	Mean	0.93	1.16	0.94	1.01
	SD	1.2	1.3	1.1	1.2
	Min	0.0	0.0	0.0	0.0
	Max	10.6	7.3	7.3	10.6
Total UPDRS at Baseline	N	134	132	138	404
	Mean	24.69	25.89	24.54	25.03
	SD	11.25	9.54	11.61	10.84
	Min	5.50	10.50	5.50	5.50
	Max	75.00	53.50	61.00	75.00
Hoehn and Yahr Stage at Baseline	N	134	132	138	404
	Mean	1.85	1.88	1.86	1.86
	SD	0.48	0.48	0.50	0.48
	Min	1.00	1.00	1.00	1.00
	Max	3.00	3.00	3.00	3.00

Table 6. ADAGIO: Baseline PD Characteristics

ADAGIO		1 mg Delayed Start	1 mg Early Start	2 mg Delayed Start	2 mg Early Start	All
Time from Diagnosis (days)	N	298	288	295	293	1174[a]
	Mean	131.8	139.4	139.6	139.5	137.6
	SD	139.9	144.0	139.2	141.2	140.9
	Min	1.0	1.0	1.0	1.0	1.0
	Median	71.0	79.5	85.0	89.0	83.0
	Max	547.0	540.0	530.0	546.0	547.0
Total UPDRS at Baseline	N	298	288	295	293	1174
	Mean	20.25	20.57	19.93	20.83	20.39
	SD	8.76	8.40	8.11	8.80	8.52
	Min	3.0	6.5	5.0	3.5	3.0
	Median	19.0	19.0	19.0	19.5	19.0
	Max	49.5	53.0	47.0	52.5	53.0
Hoehn and Yahr Scale at Baseline	N	298	288	295	293	1174
	Mean	1.51	1.53	1.46	1.52	1.51
	SD	0.49	0.49	0.48	0.48	0.48
	Min	1.0	1.0	1.0	1.0	1.0
	Median	1.5	1.5	1.5	1.5	1.5
	Max	2.5	2.5	2.5	2.5	2.5

[a] Two patients out 1176 randomized withdrew consent prior to receiving any study drug.

6.2 Concomitant PD Medications

6.2.1 TEMPO

Anticholinergics, but no other anti-PD medication, were allowed in the PC phase of the TEMPO study. Only a few patients received anticholinergics in the PC phase.

During the active-treatment phase of the TEMPO study, about a third of the patients in each treatment group (32.3% of 124 patients in the 1 mg group, 36.3% of 124 patients in the 2 mg group, and 30.3% of 132 patients in the placebo/2 mg group) required concomitant anti-PD medications (Appendix B; Table B5). UPDRS measurements taken while on anti-PD medications were not included in any TEMPO efficacy analyses.

6.2.2 ADAGIO

As previously discussed (Section 5.1.2), the use of anti-PD medications other than study drug was not permitted during the ADAGIO study. Patients who needed additional anti-PD drugs in the PC phase were transferred to the active-treatment phase, however, their UPDRS was used until the day they transferred. Sixteen (1.4%) patients terminated the PC phase due to need for an anti-PD drug and did not transfer to the active-treatment phase (Appendix B, Table B3). Patients who required anti-PD drugs in addition to study drug in the active-treatment phase were withdrawn from the study; however, their UPDRS was used until the day they withdrew (Table 8).

6.3 Patient Disposition

6.3.1 TEMPO

In TEMPO, 22 (of the 404; 5.4%) randomized patients discontinued the study prematurely during the PC phase (Table 7). The most common reason patients prematurely terminated from the PC phase was due to adverse events (AEs) (Table B1, Appendix B).

Table 7. TEMPO: Patient Disposition

TEMPO	1 mg Early Start		2 mg Early Start		2 mg Delayed Start		All	
	n	%	n	%	n	%	n	%
Placebo-Controlled Phase								
Received study medication	134	100.0	132	100.0	138	100.0	404	100.0
Completed PC phase without need for additional PD therapy	111	82.8	105	79.5	112	81.2	328	81.2
Early transfer to active-treatment phase due to need for additional PD therapy	14	10.4	19	14.4	21	15.2	54	13.4
Premature termination during PC phase	9	6.7	8	6.1	5	3.6	22	5.4
Active-Treatment Phase								
Entered into active-treatment phase	124	100.0	124	100.0	132	100.0	380	100.0
Completed the study	120	96.8	118	95.2	122	92.4	360	94.7
Premature termination during active-treatment phase	4	3.2	6	4.8	10	7.6	20	5.3

A total of 382 patients completed the PC phase, out of whom, 54 patients transferred early to the active-treatment phase due to need for additional PD (levodopa) therapy. (Patients who failed to complete the PC phase due to a need for levodopa and continued into the active-treatment phase were not considered as early withdrawals). All but 2 patients (a total of 380 patients) continued into the active-treatment phase (Table 7), with 360 patients completing – 120 (96.8% of 124 patients) in the 1 mg early-start group, 118 (95.2% of 124 patients) in the 2 mg early-start group, and 122 (92.4% of 132) patients in the 2 mg delayed-start group (who were randomized to placebo in the first phase of the study). AEs were the reason for premature discontinuation from the active-treatment phase for 0, 2 (1.6%), and 3 (2.3% of patients in the respective treatment groups (Table B2, Appendix B).

6.3.1.1 ADAGIO

In the ADAGIO study, 83 (7.1%) of the 1174 randomized patients who received at least one dose of study medication terminated prematurely during the PC phase (Table 8). The most common reason for premature termination during the PC phase was due to an AE, with an overall rate that was similar across groups (Table B3, Appendix B). A higher proportion of patients in the combined placebo (i.e., delayed

start) groups (20%) required additional anti-PD therapy and was transferred early to the active-treatment phase of the study, as compared to the active rasagiline (early start) groups (10%).

A total of 1091 (92.9%) patients entered The active-treatment phase of the ADAGIO study (Table 8).

Table 8. ADAGIO: Patient Disposition

ADAGIO	1 mg Delayed Start N=298		1 mg Early Start N=288		2 mg Delayed Start N=295		2 mg Early Start N=293		All N=1174	
	n	%	n	%	n	%	n	%	n	%
Placebo-Controlled Phase										
Received study medication	298	100.0	288	100.0	295	100.0	293	100.0	1174	100.0
Entered into active-treatment phase after completing PC phase	211	70.8	245	85.1	216	73.2	242	82.6	914	77.9
Early transfer from PC phase to active-treatment phase	59	19.8	28	9.7	59	20.0	31	10.6	177	15.1
Premature termination in PC phase	28	9.4	15	5.2	20	6.8	20	6.8	83	7.1
Active-Treatment Phase										
Entered into active-treatment phase	270	100.0	273	100.0	275	100.0	273	100.0	1091	100.0
Completed the study	231	85.6	238	87.2	241	87.6	244	89.4	954	87.4
Premature termination during active-treatment phase	39	14.4	35	12.8	34	12.4	29	10.6	137	12.6

The need for additional anti-PD therapy was the most common reason for premature termination from the active-treatment phase – 9.1% of all patients, with no systematic difference across the treatment groups (range, 8.1% to 9.6%). A similar proportion of patients discontinued the active-treatment phase due to AEs (Table B4, Appendix B).

6.4 Efficacy Results

6.4.1 Data Analysis Sets

6.4.1.1 TEMPO

The efficacy cohort for the 52-week analysis of TEMPO included all patients with at least one UPDRS measurement in the active-treatment phase. Thus, the analysis was based on 371 out of 380 (91.8%) patients who entered the active-treatment phase (Table 9).

Table 9. TEMPO: Disposition of Patients in Data Analysis Sets

TEMPO	1 mg Early Start	2 mg Early Start	2 mg Delayed Start	All
Randomized	134	132	138	404
Efficacy Analysis of Active-Treatment Phase (at least 1 UPDRS measurement in the active-treatment phase without actual anti-PD therapy)	122 (91.0%)	119 (90.2%)	130 (94.2%)	371 (91.8%)

6.4.1.2 ADAGIO

Table 10 shows that 10 patients were excluded from the analysis dataset for Hypothesis #1 (mITT Data Analysis Set). An additional 168 patients were excluded from the ACTE analysis set for Hypotheses #2 and #3, of whom 57 patients had early transfer to the active-treatment phase prior to week 24 (20 patients in the 1 mg delayed-start group, 15 patients in the 2 mg delayed-start group, and 12 and 10 patients in the 1 mg and 2 mg early-start groups, respectively). Overall, the ACTE data analysis set included 996 patients (84.8% of the study ITT data set).

Table 10. ADAGIO: Disposition of Patients in Data Analysis Sets

ADAGIO	1 mg Delayed Start	1 mg Early Start	2 mg Delayed Start	2 mg Early Start	All
Randomized	**300**	**288**	**295**	**293**	**1176**
ET due to withdrawal of consent prior to first dose of study drug	2	0	0	0	2
Study ITT	**298 (100.0%)**	**288 (100.0%)**	**295 (100.0%)**	**293 (100.0%)**	**1174 (100.0%)**
ET due to adverse event	0	0	1	3	4
ET due to withdrew consent	2	1	1	0	4
ET due to lost to follow up	1	1	0	0	2
Modified ITT for Hypothesis #1	**295 (99.0%)**	**286 (99.3%)**	**293 (99.3%)**	**290 (99.0%)**	**1164[a] (99.2%)**
Early transfer to active, pre-week 24	20	12	15	10	57
ET due to need for add PD therapy	18	9	9	6	42
ET due to adverse event	8	11	13	9	41
ET due to withdrew consent	9	3	5	3	20
ET due to Other	2	0	2	4	8
ACTE for Hypotheses #2 and #3	**238 (79.9%)**	**251 (87.2%)**	**249 (84.4%)**	**258 (88.0%)**	**996[b] (84.8%)**
Early transfer to active weeks 24-34	29	7	24	10	70
ET due to need for add PD therapy	13	15	15	16	59
ET due to withdrew consent	6	2	1	2	11
ET due to adverse event	1	3	2	2	8
Active-treatment phase <34 weeks, not ET	1	2	2	0	5
ET due to Other	0	1	1	1	3
Completers Data Analysis Set	**188 (63.1%)**	**221 (76.7%)**	**204 (69.2%)**	**227 (77.5%)**	**840 (71.6%)**
Received disallowed medication	3	0	1	0	4
Compliance <80%	1	0	0	1	2
Per Protocol Data Analysis Set	**184 (61.7%)**	**221 (76.7%)**	**203 (68.8%)**	**226 (77.1%)**	**834 (71%)**

ACTE=ACTive Efficacy (data analysis set), ET=early termination, ITT=intent-to-treat, PD=Parkinson's disease.

a. 10 patients excluded from study ITT data set.

b. 168 patients excluded from ACTE data set.

An assessment of baseline UPDRS profile for the 996 ADAGIO subjects comprising the ACTE data analysis set in comparison to the 168 subjects not included in the ACTE data analysis set is presented in Table 11. It is evident that subjects not included in the ACTE dataset, due to early termination from the PC phase or early transfer to the active-treatment phase, have higher baseline UPDRS in all treatment groups compared to those in the ACTE dataset, meaning they are at a slightly more advanced stage of the disease. Moreover (as described before), early transfer to the active-treatment phase was two-fold greater in the delayed-start groups (placebo) compared to the early-start rasagiline groups. As a result, although all groups were similar at baseline for ITT cohort, in the ACTE datasets baseline UPDRS of those in early active treatment (either 1 mg or 2 mg) is more than one point higher than those who were previously on placebo (delayed-start).

Table 11. ADAGIO: Descriptive Statistics of Baseline UPDRS by Analysis Datasets

ADAGIO		1 mg Delayed Start	1 mg Early Start	2 mg Delayed Start	2 mg Early Start	All
Subjects in mITT dataset*	N	295	286	293	290	1164
	Mean	20.29	20.59	19.91	20.76	20.38
	SD	8.77	8.42	8.09	8.79	8.52
	Min	3	7	5	4	3
	Median	19	19	19	20	19
	Max	50	53	47	53	53
Subjects in ACTE dataset	N	238	251	249	258	996
	Mean	19.10	20.53	19.24	20.27	19.80
	SD	8.07	8.45	7.87	8.45	8.23
	Min	3	7	5	4	3
	Median	18	19	18	19	19
	Max	49	53	47	52	53
Subjects Excluded from ACTE dataset	N	57	35	44	32	168
	Mean	25.27	21.00	23.70	24.77	23.88
	SD	9.83	8.31	8.35	10.46	9.34
	Min	10	7	6	7	6
	Median	25	22	25	23	24
	Max	50	43	38	53	53

ACTE=ACTive Efficacy (data analysis set).
* Excluding subjects who did not have any post-baseline UPDRS in the PC Phase.

Missing UPDRS observations in ADAGIO

Patients completing the trial per protocol should have had 3 post-baseline UPDRS assessments during the placebo-controlled phase and an additional 6 UPDRS assessments during the active-treatment phase for analysis purposes. Thus, altogether 10566 UPDRS assessments should have been made (9 x 1174).

A total of 306 subjects (26.1%) had at least one missing UPDRS assessment (see Table 12).

Table 12. ADAGIO: Distribution of Number of Patients with at least one Missing UPDRS Observation – during Entire Study

ADAGIO	Treatment Group								All	
	1mg Delayed Start		1mg Early Start		2mg Delayed Start		2mg Early Start			
	N	%	N	%	N	%	N	%	N	%
Missing	94	31.5	68	23.6	77	26.1	67	22.9	306	26.1
Not Missing	204	68.5	220	76.4	218	73.9	226	77.1	868	73.9
All	298	100.0	288	100.0	295	100.0	293	100.0	1174	100.0

In the PC phase, 92.9% of the UPDRS observations were not missing (Table 13); 3.7% of the observations were missing due to early transfer to the Active-treatment phase with a larger percentage of missing data in the delayed start arms.

Table 13. ADAGIO: Distribution of Number of UPDRS Missing Observations by Reason for Missing – during Placebo-Controlled Phase

ADAGIO	Treatment Group								All	
	1mg Delayed Start		1mg Early Start		2mg Delayed Start		2mg Early Start			
	N	%	N	%	N	%	N	%	N	%
Not Missing	807	90.3	821	95.0	815	92.1	829	94.3	3272	92.9
Missing Due to Early Termination	44	4.9	20	2.3	36	4.1	30	3.4	130	3.7
Missing Due to Early Transfer	43	4.8	22	2.5	34	3.8	19	2.2	118	3.4
Other Missing	.	.	1	0.1	.	.	1	0.1	2	0.1
All	894	100.0	864	100.0	885	100.0	879	100.0	3522	100.0

In the active-treatment phase, 85.7% of the UPDRS observations were non-missing (see Table 14);however, 11.8% were non-missing following early transfer with a larger percentage in the delayed-start arms. There was also a larger percentage of missing data due to early termination in the delayed-start groups.

Table 14. ADAGIO: Distribution of Number of UPDRS Missing Observations by Reason for Missing – during Active-treatment phase

ADAGIO	Treatment Group								All	
	1mg Delayed Start		1mg Early Start		2mg Delayed Start		2mg Early Start			
	N	%	N	%	N	%	N	%	N	%
Not Missing	1180	66.0	1389	80.4	1246	70.4	1393	79.2	5208	73.9
Not Missing for patients of Early Transfer	283	15.8	119	6.9	284	16.0	145	8.2	831	11.8
Missing Due to Early Termination	320	17.9	214	12.4	238	13.4	210	11.9	982	13.9
Other Missing	5	0.3	6	0.3	2	0.1	10	0.6	23	0.3
All	1788	100.0	1728	100.0	1770	100.0	1758	100.0	7044	100.0

6.4.1.3 TEMPO Analysis with ADAGIO Endpoints

Table 15 shows the number of patients in each treatment group and the reasons for exclusion from the re-analysis according to ADAGIO.

In the analysis of TEMPO according to ADAGIO, 21 of the 22 patients who prematurely terminated from the PC phase of the trial did not have UPDRS data from week 14 and onwards and were excluded from the analysis dataset for Hypothesis #1, while those who had week 14 UPDRS data were included. A total of 380 patients entered the active-treatment phase. However, only 279 patients fulfilled the ADAGIO condition of exposure to treatment in the PC phase of at least 24 weeks with at least one UPDRS measurement from Week 42 and on. Therefore, the analysis for Hypotheses #2 and #3 was based on a data set of 279 patients (i.e., 31% were excluded from the analyses of Hypotheses #2 and #3).

Defining the ACTE data set according to the ADAGIO rules was stricter for the TEMPO patient population, which had a more advanced PD. These rules required completion of 24 weeks in the PC phase, which is equivalent to completion of the PC phase. Thus, patients who transferred to the active-treatment phase prior to week 24 were not included. This requirement resulted in the higher proportion of patients excluded from the ACTE dataset compared to ADAGIO.

Table 15. TEMPO: Disposition of Patients in Data Analysis Sets

TEMPO	1 mg Early Start	2 mg Early Start	2 mg Delayed Start	All
Randomized	134	132	138	404
Reanalysis of TEMPO Based on ADAGIO:				
Study ITT	134 (100.0%)	132 (100.0%)	138 (100.0%)	404(100.0%)
No UPDRS data at weeks 14, 20, or 26	9	9	3	21[a]
mITT for Hypothesis #1	125 (93.3%)	123 (93.2%)	135 (97.8%)	383 (94.8%)
Early transfer to active-treatment phase pre-week 24	12	17	21	50
Transfer after week 24: No UPDRS data at weeks 42 or 52	17	17	20	54
ACTE for Hypotheses #2 and #3	96 (71.6%)	89 (67.4%)	94 (68.1%)	279 (69.1%)

a. 22 patients terminated the PC phase prematurely, but one of them had data from week 14 onward.
ACTE=ACTive Efficacy (data analysis set), ITT=intent-to-treat, PD=Parkinson's disease, UPDRS=Parkinson's Disease Rating Scale.

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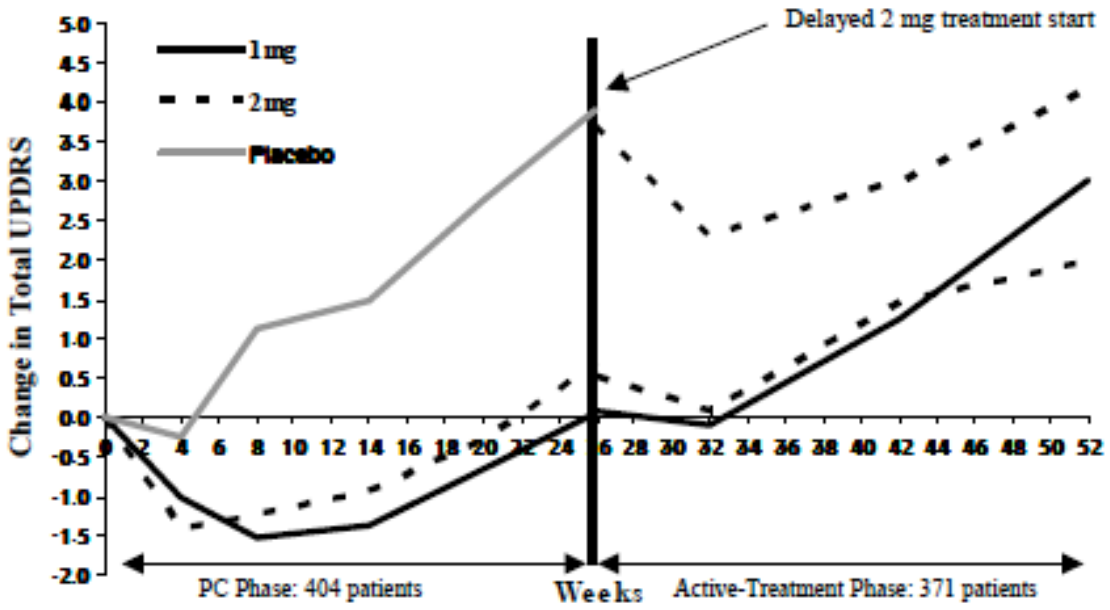
6.4.2 TEMPO 52-Week Analysis Results

The 52-week total UPDRS (LOCF) mean (±SD) scores for the 371 participants were 27.45 (14.18), 27.10 (11.90), and 28.02 (14.17) for the 1 mg early-start, 2 mg early-start, and 2 mg delayed-start groups, respectively. According to the predefined analysis of the exploratory endpoint for the 52-week TEMPO study, the mean (±SD) changes in UPDRS from baseline to last observed value were 3.01 (8.26), 1.97 (7.49) and 4.17 (8.83) for the 1 and 2 mg early-start groups and the 2 mg delayed-start groups, respectively (Figure 6).

Figure 6. TEMPO Original 52-Week Analysis: Mean Change from Baseline in Total UPDRS (LOCF)



Based on the LOCF method to account for missing data, the difference in adjusted means between each of the rasagiline early treatment groups and the 2 mg delayed-start group (two contrasts) was statistically significant (-1.85 for 1 mg, p=0.046 and -2.08 for 2 mg, p=0.024). Due to the presence of few outliers, a nonparametric analysis was performed (median changes from baseline to LOV were 3, 1.5 and 3.5 for the 1 and 2 mg early-start groups and the 2 mg delayed-start groups, respectively). The model applied on ranks yielded a notable difference (p-value=0.024) for the comparison of early vs. delayed 2 mg treatment. No appreciable difference was shown for the comparison of 1 mg early-start and 2 mg delayed-start groups (p-value=0.482).

The TEMPO study was conducted by the Parkinson's Study Group (PSG). This group's statisticians independently analyzed the TEMPO data and published their results in The Archives of Neurology in 2004[72]: The effect of treatment (calculated by the difference between adjusted means of the ANCOVA model) on total UPDRS score comparing the 2 mg early-start and 2 mg delayed-start groups was -2.29 units [95% CI, -4.11 to -0.48 units]; p-value=0.01. Comparison of the 1 mg early-start and 2 mg delayed-start groups yielded -1.82 units [95% CI, −3.64 to 0.01 units]; p-value=0.05.

6.4.3 ADAGIO Efficacy Results

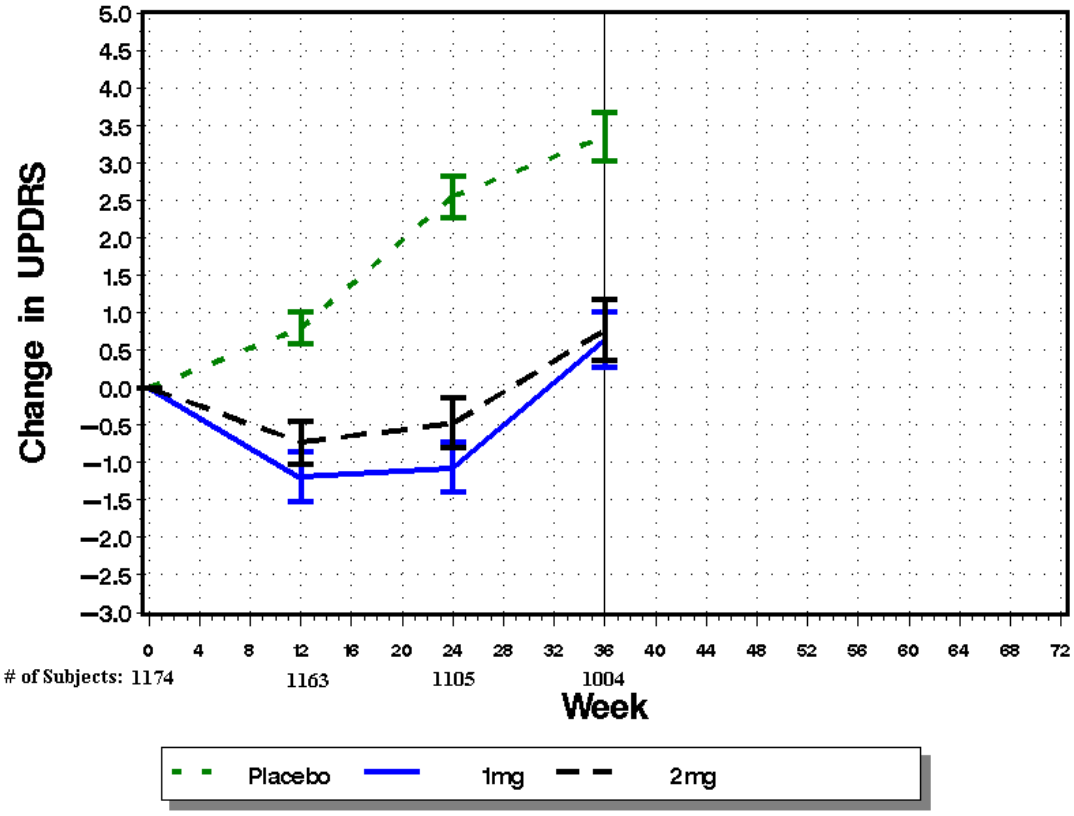
6.4.3.1 ADAGIO UPDRS Change Over Time

Mean and standard error of the changes from baseline in Total UPDRS scores for the modified ITT data analysis set during the placebo-controlled phase are displayed graphically in Figure 7. As can be seen in the figure, UPDRS scores for the rasagiline-treated groups separate from those of the pooled placebo group, reflecting a smaller deterioration of UPDRS in rasagiline-treated subjects. The groups are already separated at 12 weeks, presumably due mainly to symptomatic activity, and this separation is larger at 36 weeks.

Mean and standard error of the changes from baseline in UPDRS scores for the 1 mg rasagiline early and delayed-start for patients included in the ACTE data analysis set during the placebo-controlled and active-treatment phases are displayed graphically in Figure 8. It is clearly seen in the figure, that a separation of UPDRS scores is maintained throughout the second study phase, even though both groups received active treatment during this phase.

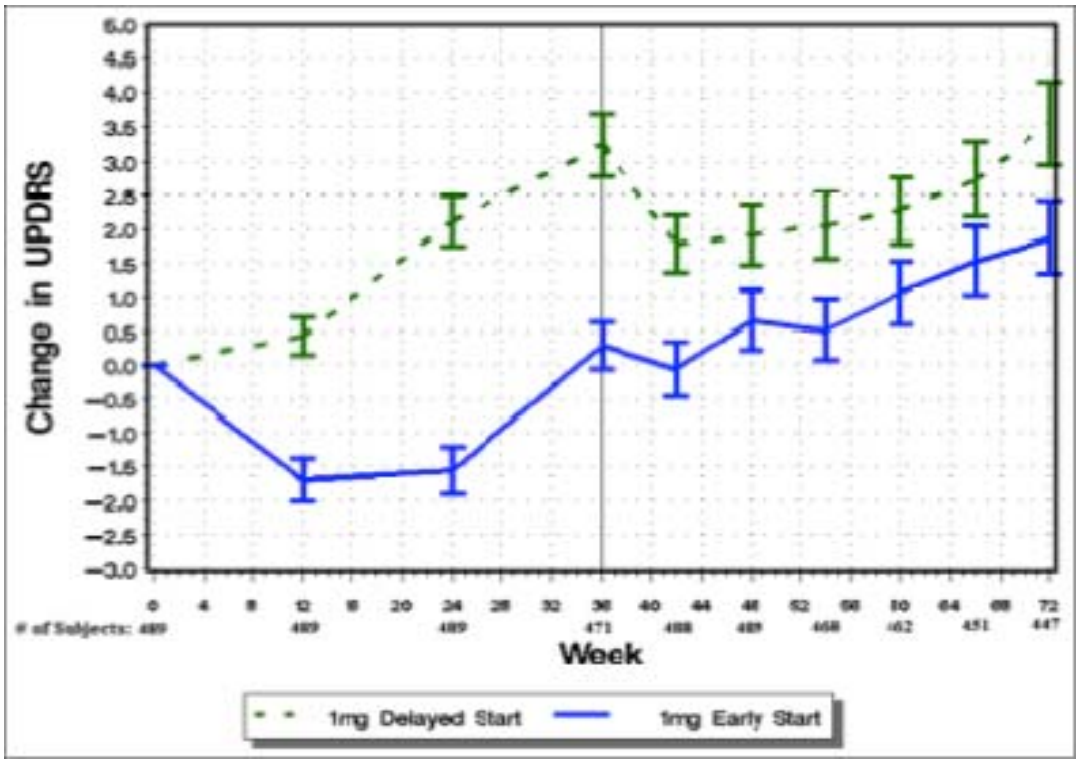
Mean and standard error of the changes from baseline in UPDRS scores for the 2 mg rasagiline early and delayed-start for patients included in the ACTE data analysis set during the placebo-controlled and active-treatment phases are displayed graphically in Figure 9. The separation of UPDRS scores seen during the placebo-controlled phase is not maintained throughout the second study phase for this dose.

Figure 7. Change from Baseline in Total UPDRS Score during Placebo-Controlled Phase – mITT Data Analysis Set



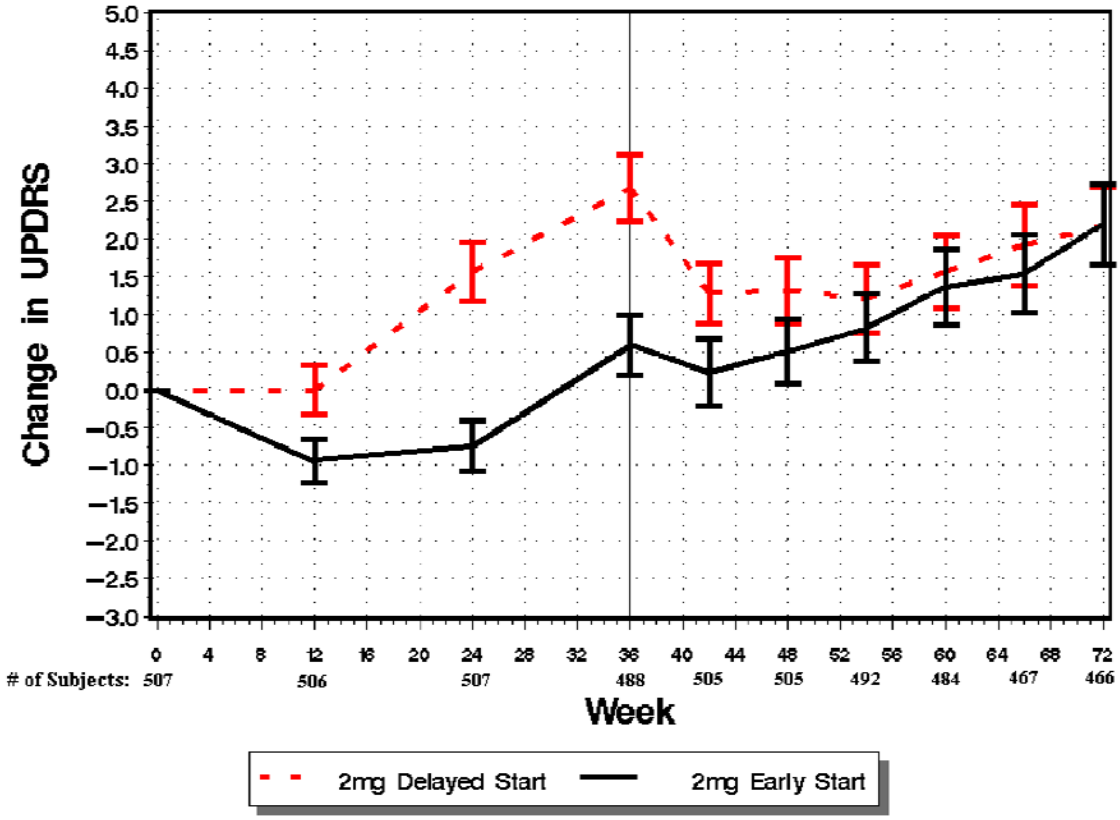
Numbers represent the number of subjects per week.

Figure 8. Change from Baseline in Total UPDRS Score during Placebo-Controlled and Active-Treatment Phases for Rasagiline 1 mg – ACTE Data Analysis Set



Numbers represent the number of patients per week. The larger number of patients in week 42 compared to week 36 was due to the early transfer of patients from the PC phase to the active-treatment phase.

Figure 9. Change from Baseline in Total UPDRS Score during Placebo-Controlled and Active-Treatment Phases for Rasagiline 2 mg – ACTE Data Analysis Set



Numbers represent the number of patients per week. The larger number of patients in week 42 compared to week 36 was due to the early transfer of patients from the PC phase to the active-treatment phase.

6.4.3.2 ADAGIO: Results of Primary Analysis

Hypothesis #1: superiority of rasagiline over placebo in the PC phase from week 12 to week 36 for the rate of change in UPDRS.

Results of the SAP-defined primary analysis are presented in Table 16. A point estimate of -0.046 UPDRS units/week was obtained for the difference between the 1 mg early-start rasagiline and placebo groups in the rate of UPDRS deterioration (p=0.0133). A point estimate of -0.072 UPDRS units/week was obtained for the difference between placebo and the 2 mg early-start rasagiline group in the rate of UPDRS deterioration (p=0.0001). The estimated differences for the 1 mg and 2 mg groups from placebo correspond to 2.4 and 3.7 UPDRS units/year, respectively.

Table 16. ADAGIO: Hypothesis #1: Comparison of Slopes from Week 12 to 36

Group	Estimate (95% CI)	Difference Between Groups (95% CI)	*p*-Value for Difference
Placebo	0.139 (0.117,0.160)	NA	NA
1 mg	0.093 (0.063,0.122)	-0.046 (-0.083, -0.010)	0.0133
2 mg	0.066 (0.037, 0.096)	-0.072 (-0.109, -0.036)	0.0001

Test for Linearity

The primary model for Hypothesis #1 assumes linearity over Weeks 12 - 36 in the PC phase. A linearity test was performed post-hoc, and following the result an alternative categorical analysis for deriving separation in deterioration that requires no assumption of linearity was conducted *post-hoc*. In the alternative analysis, the slope difference between each of the Rasagiline treated groups and placebo group is replaced by testing whether the differences between each active group and placebo group at Week 36 are larger than the differences between the active and placebo groups at Week 12.

Results of the various sensitivity analyses are presented in Table 17. As can be seen in the table, the analyses based on the completers and per protocol populations, as well as the analyses using multiple

imputation, yielded results that were consistent with the primary. In addition, the alternative categorical analysis implemented due to concerns over linearity yielded consistent finding with the linear approach.

Table 17. ADAGIO: Hypothesis #1: Summary of Sensitivity Analyses

Data Analysis Set	Analysis	Rasagiline Dose Level	Difference Between Groups	*p*-value for Difference	95% CI
CO	Rate of change during PC phase, RM	1 mg	-0.033	0.0645	-0.069, 0.002
		2 mg	-0.061	0.0007	-0.096, -0.026
PP	Rate of change during PC phase, RM	1 mg	-0.037	0.0414	-0.072, -0.001
		2 mg	-0.065	0.0003	-0.100, -0.030
Imputed ITT	Rate of change during PC phase, RM, multiple imputation	1 mg	-0.045	0.0158	-0.081, -0.009
		2 mg	-0.068	0.0002	-0.103, -0.032
ITT	Alternative categorical	1 mg	-1.043	0.0196	-1.918, -0.168
		2 mg	-1.668	0.0002	-2.541, -0.794
CO	Alternative categorical	1 mg	-0.799	0.0659	-1.650, 0.053
		2 mg	-1.463	0.0007	-2.307, -0.620
PP	Alternative categorical	1 mg	-0.873	0.0605	-1.785, 0.038
		2 mg	-1.553	0.0008	-2.458, -0.648

CO=completers cohort, PP=per protocol ITT=intent-to-treat, RM=repeated measures,

Hypothesis #2: Superiority of early-start over delayed-start of rasagiline from baseline to Week 72 for change in UPDRS

Analysis based on original SAP (March 2007)

As detailed in Section 5.2.2.3, the primary analysis of Hypothesis #2 in the original SAP, based on mean change from baseline in Total UPDRS across Weeks 48-72 (active-treatment phase) derived from the repeated measures ANCOVA model, for which the study was powered, demonstrated a benefit of early 1 mg treatment over delayed treatment.

Table 18. ADAGIO: Hypothesis #2: Comparison of Mean Change in UPDRS across Weeks 48-72 – Based on Original SAP

Group	Estimate (95% CI)	Early-Delayed Estimate (95% CI)	*p*-Value for Difference
1 mg delayed-start	3.149 (2.344, 3.954)	-1.408 (-2.500, -0.317)	0.0115
1 mg early-start	1.741 (0.969, 2.512)		
2 mg delayed-start	2.170 (1.395, 2.945)	-0.272 (-1.338, 0.794)	0.6164
2 mg early-start	1.898 (1.130, 2.665)		

Mixed Model Repeated Measures Model with categorical week in trial using Unstructured Covariance Matrix

Primary Efficacy Analysis Based on Final SAP

Results for the primary analysis for Hypothesis #2, as described in the final SAP (combined data set), are presented in Table 19.

Table 19. ADAGIO: Hypothesis #2: Comparison of Change in UPDRS at Week 72 Based on Final SAP (Combined Dataset)

	Combined Dataset		
Group	Estimate (95% CI)	Early-Delayed Estimate (95% CI)	*p*-Value for Difference
1 mg delayed-start	4.421 (3.379, 5.462)	-1.425 (-2.853, 0.004)	0.0506
1 mg early-start	2.996 (1.993, 3.999)		
2 mg delayed-start	3.022 (2.015, 4.029)	0.179 (-1.218, 1.576)	0.8014
2 mg early-start	3.201 (2.207, 4.195)		

Repeated Measures Mixed Linear using Unstructured Covariance Matrix; baseline UPDRS and center adjusted
CI =confidence interval

A larger deterioration from baseline to Week 72 was evident for the 1 mg delayed-start group (4.42 UPDRS units) compared to the 1 mg early-start group (2.996 UPDRS units). A point estimate of -1.425 UPDRS units was obtained for the difference between the 1 mg early-start and 1 mg delayed-start treatment groups in the change from baseline in UPDRS (p=0.0506). No difference in deterioration from baseline to Week 72 was evident between the 2 mg early-start and delayed-start groups. Thus, the null hypothesis for the rasagiline 2 mg delayed-start to early-start comparison was not rejected. Therefore, the

p-value of 0.0506 for the 1 mg delayed-start to early-start comparison was not statistically significant at an alpha level of 2.5% dictated by the method of adjustment for multiple comparisons.

Results Based on the Separate Datasets

Table 20 presents the findings for Hypotheses #2 based on analysis of separate datasets, as described in Section 5.2.2.3.

Table 20. ADAGIO: Hypothesis #2: Comparison of Change in UPDRS at Week 72 (Separate Datasets)

	Separate Datasets		
Group	**Estimate (95% CI)**	**Early-Delayed Estimate (95% CI)**	***p*-Value for Difference**
1 mg delayed-start	4.495 (3.405, 5.585)	-1.680 (-3.148, -0.212)	0.0250
1 mg early-start	2.815 (1.777, 3.853)		
2 mg delayed-start	3.111 (2.128, 4.093)	0.356 (-0.989, 1.702)	0.6028
2 mg early-start	3.467 (2.491, 4.444)		

CI =confidence interval, UPDRS=Unified Parkinson's Disease Rating Scale.
Repeated Measures Mixed Linear using Unstructured Covariance Matrix; baseline UPDRS and center adjusted.

A larger deterioration from baseline to Week 72 was evident for the 1 mg delayed-start group (4.495 UPDRS units) compared to the 1 mg early-start group (2.815 UPDRS units). A point estimate of -1.680 UPDRS units was obtained for the difference between the 1 mg early-start and 1 mg delayed-start treatment groups in the change from baseline in UPDRS (*p*=0.0250). Similar deteriorations from baseline at Week 72 were evident for both the 2 mg early-start and 2 mg delayed-start groups.

When the interaction terms of dose level by baseline UPDRS and dose level by center were added to the model, results derived from the combined data set were similar to those derived from the separate data sets: treatment effect (95% CI) = -1.606 (-2.949, -0.264); p-value= 0.0191. As previously stated, it is because of these interactions that the analysis of Hypothesis #2 was applied to separate data sets.

Sensitivity Analyses

Table 21 presents the results of all sensitivity analyses performed for combined and separate datasets. There were no appreciable differences seen between the 2 mg early and delayed groups in any of the analyses. Results were consistently positive for the 1 mg early start group compared to the 1 mg delayed start group.

The most conservative analysis from a point estimate perspective is the one where all missing values were imputed using the means of the delayed groups. In this highly conservative analysis, the early group had a benefit of -1.2. In all other analyses including those previously reported, the point estimates averaged about -1.7 ranging from -1.4 to -1.9.

Table 21. ADAGIO Study: Hypothesis #2: Summary of Sensitivity Analyses

Data Analysis Set	Analysis	Rasagiline Dose Level	Difference Between Groups	*p*-value for Difference	95% CI
CO	Change from baseline to Week 72, RM, separate data sets	1 mg	-1.592	0.0374	-3.090, -0.093
		2 mg	-0.088	0.8974	-1.426, 1.250
PP	Change from baseline to Week 72, RM, separate data sets	1 mg	-1.594	0.0392	-3.108, -0.079
		2 mg	-0.024	0.9723	-1.359, 1.312
Imputed ITT	Change from baseline to Week 72, RM, multiple imputation, separate data sets	1 mg	-1.832	0.0105	-3.232, -0.432
		2 mg	-0.435	0.5308	-1.802, 0.931
Imputed ITT	Change from baseline to Week 72, RM, multiple imputation, combined data set	1 mg	-1.703	0.0127	-3.040, -0.366
		2 mg	-0.564	0.4143	-1.922, 0.794
Imputed ITT	Change from baseline to Week 72, RM, imputation using means of delayed groups, separate data sets	1 mg	-1.192	0.0422	-2.343, -0.042
		2 mg	0.053	0.9203	-0.987, 1.093
ITT	Change from baseline to Week 72, RM, Weeks 12 to 72, observed data, separate data sets	1 mg	-1.673	0.0295	-3.179, -0.168
		2 mg	-0.236	0.7407	-1.637, 1.165
ITT	Change from baseline to Week 72, RM, Weeks 12 to 72, observed data combined data set	1 mg	-1.611	0.0305	-3.069, -0.152
		2 mg	-0.266	0.7175	-1.710, 1.178
ACTE	Change from baseline to Week 72, ANCOVA with LOCF, separate data sets	1 mg	-1.755	0.0119	-3.121, -0.389
		2 mg	0.0785	0.9033	-1.190, 1.347
ACTE	Change from baseline to Week 72, ANCOVA with LOCF, rank transformation, separate data sets	1 mg	NA	0.0320	NA
		2 mg	NA	0.7829	NA
ACTE-Matched Pairs subset	Change from baseline to Week 72, RM, Adjusted Means, combined data set	1 mg	-1.515	0.0513	-3.039, 0.008
		2 mg	0.016	0.9826	-1.460, 1.493
ACTE	Change from baseline to Week 72, RM, Propensity Analysis: Propensity score as continuous covariate, separate data sets	1 mg	-1.916	0.0142	-3.446, -0.386
		2 mg	0.460	0.5247	-0.960, 1.879
ACTE	Change from baseline to Week 72, RM, Propensity Analysis: Propensity score as categorical variable (based on quintiles), separate data sets	1 mg	-1.862	0.0249	-3.488, -0.236
		2 mg	0.366	0.6117	-1.050, 1.783

Hypothesis #3: Non-inferiority of early-start to delayed-start in the active-treatment phase from Week 48 to 72 for the rate of change in UPDRS.

Results for the primary analyses of for Hypothesis #3, as described in the final SAP (combined data set), are presented in Table 22. Analyses were not formally interpreted for Hypothesis #3 based on the Hypothesis #2 outcome (not reaching statistical significance); however, the upper CI did not exceed the non-inferiority margin of 0.15 for both 1 and 2 mg.

For 1 mg, the point estimate for a difference in slopes is essentially 0 and the CI excludes any difference larger than 0.027. This difference translates to 1.4 UPDRS points / year.

Table 22. ADAGIO: Hypothesis #3: Comparison of Slopes from Week 48 to 72 Analysis – Based on SAP (Combined Dataset)

ADAGIO	Combined Dataset	
Group	Estimate (95% CI)	Early-Delayed Estimate (90% CI)
1 mg delayed-start	0.085 (0.061, 0.109)	-0.001 (-0.029, 0.027)
1 mg early-start	0.083 (0.060, 0.107)	
2 mg delayed-start	0.063 (0.039, 0.086)	0.030 (0.003, 0.058)
2 mg early-start	0.093 (0.070, 0.116)	

Repeated Measures Mixed Linear using Unstructured Covariance Matrix; baseline UPDRS and center adjusted
CI =confidence interval

Primary analysis of Hypothesis #3 based on separate datasets, is presented in Table 23; the upper CI did not exceed the non-inferiority margin of 0.15 for both 1 and 2 mg.

For 1mg, the point estimate for a difference in slopes is essentially 0 and the CI excludes any difference larger than 0.036. This difference translates to 1.9 UPDRS points / year.

Table 23. ADAGIO: Hypothesis #3: Comparison of Slopes from Week 48 to 72 Analysis – (Separate Datasets)

	Separate Datasets	
Group	**Estimate (95% CI)**	**Early-Delayed Estimate (90% CI)**
1 mg delayed-start	0.085 (0.054, 0.116)	0.000 (-0.036, 0.036)
1 mg early-start	0.085 (0.055, 0.115)	
2 mg delayed-start	0.065 (0.037, 0.094)	0.029 (-0.005, 0.062)
2 mg early-start	0.094 (0.066, 0.122)	

Repeated Measures Mixed Linear using Unstructured Covariance Matrix; baseline UPDRS and center adjusted
CI =confidence interval

Results of sensitivity analyses are presented in Table 24. In all models the upper CI did not exceed 0.15 for both 1 and 2 mg.

Table 24. ADAGIO: Hypothesis #3: Sensitivity Analyses

Data Analysis Set	Analysis	Rasagiline Dose Level	Treatment Effect	90% CI
CO	Rate of change from Week 48, RM, separate data sets	1 mg	-0.011	-0.047, 0.025
		2 mg	0.021	-0.010, 0.053
PP	Rate of change from Week 48, RM, separate data sets	1 mg	-0.011	-0.047, 0.024
		2 mg	0.022	-0.010, 0.053
Imputed ITT	Rate of change from Week 48, RM, multiple imputation, separate data sets	1 mg	0.001	-0.042, 0.043
		2 mg	0.023	-0.017, 0.062
Imputed ITT	Rate of change from Week 48, RM, multiple imputation, combined data set	1 mg	0.001	-0.039, 0.041
		2 mg	0.023	-0.015, 0.060
Imputed ITT	Rate of change from Week 48, RM, imputation using means of delayed groups, separate data set	1 mg	0.005	-0.026, 0.036
		2 mg	0.022	-0.008, 0.052

RM = repeated measures

Summary of Results for the 3 Hypotheses

As seen by the primary model and the various sensitivity analyses applied on Hypothesis #1, the rates of UPDRS deterioration were significantly lower in both rasagiline groups.

Early treatment with 1 mg showed a consistent benefit over delayed treatment as reflected in the results of Hypothesis #2 based on the various models applied to the primary analysis. Such benefit was not evident in early treatment with 2 mg.

In all models used for Hypothesis #3, the upper CI did not exceed the predefined non-inferiority margin of 0.15 for both 1 and 2 mg. The CI's also all excluded differences in slopes above 0.043 for 1 mg and 0.062 for 2 mg

6.4.4 UPDRS Subscale Analysis of ADAGIO

To test the hypothesis that ADL might serve as a better marker of disease progression than other sections of the UPDRS[76,77] the relative contribution to treatment effects of motor and ADL subscores at Weeks 36 and 72 were investigated.

Rasagiline 1 mg per day improved each of the UPDRS subscales between baseline and Week 36 compared with placebo (Table 25). At Week 72, an appreciable difference was recorded in the change from baseline between the early-start and delayed-start groups in the ADL subscale and motor scores, with no appreciable change in mental subscores (Table 25). The ADL component contributed 41% to the total UPDRS benefit recorded with early treatment versus delayed treatment at Week 72 compared with a 29% contribution versus placebo at Week 36 (Table 25).

Rasagiline 2 mg per day improved both UPDRS motor and ADL subscales in change from baseline to Week 36 compared with placebo (Table 25). Percentage contributions of motor and ADL subscores were similar to those of the 1 mg dose (Table 25). No appreciable differences between early-start and delayed-start groups in any of the UPDRS subscales in the change from baseline to Week 72 for the 2 mg dose were observed (Table 25).

Table 25. Effects of Treatment on UPDRS Subscores at Week 36 and Week 72

Dose Group UPDRS Subscore	Week 36 (Rasagiline vs. Placebo)	Week 72 (Early vs. Delayed Start)
Rasagiline 1 mg		
Mentation	-0.22 (0.08[a] [7%])	-0.12 (0.10 [8%])
ADL	-0.86 (0.18[b] [29%])	-0.62 (0.29[c] [41%])
Motor	-1.88 (0.35[b] [64%])	-0.76 (0.51 [51%])
Rasagiline 2 mg		
Mentation	-0.06 (0.08 [3%])	0.15 (0.08)
ADL	-0.88 (0.18[b] [28%])	-0.23 (0.25)
Motor	-2.18 (0.35[b] [70%])	0.36 (0.48)

UPDRS=Unified Parkinson's disease rating scale. ADL=activities of daily living.

a. p=0·004

b. p<0·0001

c. p=0·035.

d. Percentage contributions to total treatment effect have not been calculated for the 2 mg per day dose at week 72 because the total treatment effect was not significant.

Note: Data presented as mean (SE [percentage subscore contribution to treatment effect]).

Source: Rascol et al., 2011[78]

6.4.5 Subgroup Analyses of Primary Endpoint by PD Severity at Baseline - ADAGIO

It is difficult to explain why the 2 mg dose in the ADAGIO study did not provide benefits similar to the 1 mg dose in Hypothesis #2, particularly as this dose had positive results in the TEMPO study. There were no significant differences in baseline characteristics between the two rasagiline groups, nor was there a significant difference in dropout rates. A stronger effect of the 2 mg dose on Parkinsonian symptoms in the second phase as compared to the first phase might have masked a disease-modifying benefit associated with early-start treatment in this population.

Because the patient population had lower baseline UPDRS scores and less advanced disease than in TEMPO, the possibility was considered that a floor effect in the UPDRS may have masked a benefit of early start in this population. To address this possibility analyses for the three hypotheses comprising the

primary endpoint were further carried out for 25% of the patients with highest baseline UPDRS scores (>25.5), and for the less severe patients with baseline UPDRS ≤25.5.

In the subgroup of most severe patients (baseline UPDRS >25.5), a total of 105 patients comprised the 1 mg group and 114 patients comprised the 2 mg group. In the subgroup of less severe patients (baseline UPDRS ≤25.5), a total of 384 patients comprised the 1 mg group and 393 patients comprised the 2 mg group.

The results of the analyses for the most severe patients (baseline UPDRS >25.5) are provided in Table 26, and for the less severe patients (baseline UPDRS ≤25.5) in Table 27.

Table 26. ADAGIO: Summary of Results for Patients with Baseline UPDRS> 25.5

ADAGIO: Baseline UPDRS> 25.5			
Hypothesis #1: Comparison of Slopes from Week 12 to 36			
Group	**Estimate (95% CI)**	**Difference Between Groups (95% CI)**	***p*-Value for Difference**
Placebo	0.253 (0.196, 0.310)	NA	NA
1 mg	0.144 (0.066, 0.221)	-0.109 (-0.205, -0.013)	0.0260
2 mg	0.050 (-0.025, 0.125)	-0.203 (-0.297, -0.109)	<.0001
Hypothesis #2: Comparison of Change in UPDRS at Week 72			
Group	**Estimate (95% CI)**	**Early-Delayed Estimate (95% CI)**	***p*-Value for Difference**
1 mg delayed-start	5.409 (3.020, 7.798)	-3.404 (-6.711, -0.096)	0.0439
1 mg early-start	2.005 (-0.173, 4.183)		
2 mg delayed-start	5.086 (2.721, 7.451)	-3.626 (-7.044, -0.208)	0.0379
2 mg early-start	1.460 (-0.820, 3.741)		
Hypothesis #3: Comparison of Slopes from Week 48 to 72			
Group	**Estimate (95% CI)**	**Early-Delayed Estimate (90% CI)**	***p*-Value for Difference**
1 mg delayed-start	0.095 (0.020, 0.170)	-0.020 (-0.105, 0.066)	NA
1 mg early-start	0.075 (0.006, 0.145)		
2 mg delayed-start	0.137 (0.056, 0.219)	-0.031 (-0.126, 0.064)	NA
2 mg early-start	0.106 (0.027, 0.186)		

Among the most severe patients, results across the three hypotheses supported an effect of clinical progression. Patients in the early treatment group showed less worsening in the UPDRS score between baseline and week 72 than patients in the delayed-start group, for both doses 1 mg and 2 mg.

In the subgroup of patients with UPDRS scores ≤25.5 points at baseline (in Table 27), only the 1 mg group showed evidence of advantage of early treatment with rasagiline, even though this range of UPDRS scores may be particularly insensitive for detection using the UPDRS scale due to the aforementioned floor effect.

Table 27. ADAGIO: Summary of Results for patients with Baseline UPDRS≤ 25.5

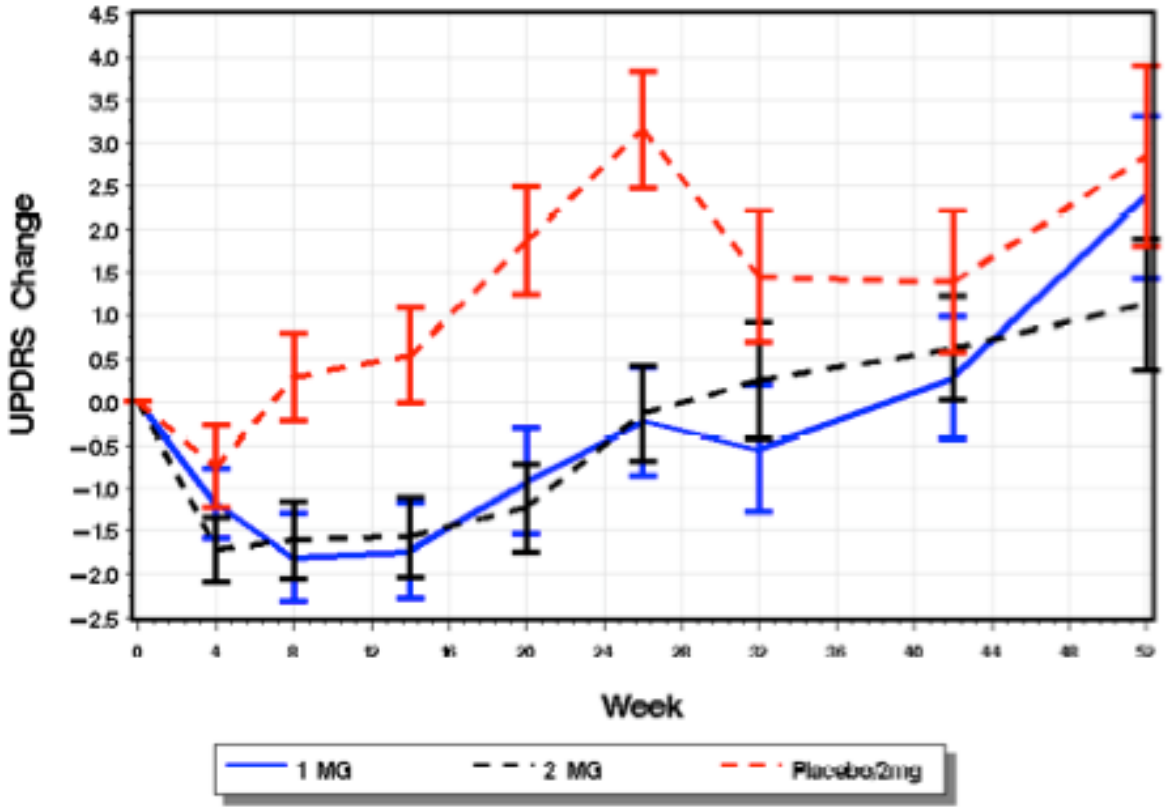
ADAGIO: Baseline UPDRS≤ 25.5			
Hypothesis #1: Comparison of Slopes from Week 12 to 36			
Group	**Estimate (95% CI)**	**Difference Between Groups (95% CI)**	***p*-Value for Difference**
Placebo	0.106 (0.084, 0.127)	NA	NA
1 mg	0.077 (0.048, 0.107)	-0.028 (-0.065, 0.009)	0.1324
2 mg	0.072(0.042, 0.102)	-0.034 (-0.071, 0.003)	0.0748
Hypothesis #2: Comparison of Change in UPDRS at Week 72			
Group	**Estimate (95% CI)**	**Early-Delayed Estimate (95% CI)**	***p*-Value for Difference**
1 mg delayed-start	4.207 (3.031, 5.024)	-1.084 (-2.387, 0.220)	0.1031
1 mg early-start	2.944 (2.013, 3.875)		
2 mg delayed-start	2.602 (1.596, 3.607)	1.102 (-0.240, 2.444)	0.1071
2 mg early-start	3.704 (2.739, 4.668)		
Hypothesis #3: Comparison of Slopes from Week 48 to 72			
Group	**Estimate (95% CI)**	**Early-Delayed Estimate (90% CI)**	***p*-Value for Difference**
1 mg delayed-start	0.082 (0.049, 0.116)	0.004 (-0.035, 0.043)	NA
1 mg early-start	0.086 (0.053, 0.119)		
2 mg delayed-start	0.046 (0.017, 0.075)	0.045 (0.011, 0.079)	NA
2 mg early-start	0.091 (0.063, 0.120)		

6.4.6 TEMPO Analysis Using ADAGIO Methodology

6.4.6.1 TEMPO UPDRS Change Over Time

Figure 10 shows mean changes from baseline in UPDRS scores for the ACTE data set during the TEMPO study. The terms under which a subject qualified to the ACTE data set were defined for ADAGIO and then applied to the TEMPO population.

Figure 10. TEMPO Reanalysis: Mean ± SE of Change from Baseline in Total UPDRS Score for Patients with at Least 24 Weeks in the PC Phase – Observed Data Without LOCF



TVP=D12232 (TEMPO) — Mean + — SE of Change in Total UPDRS Score — No LOCF — For Patients with at least 24 Weeks in the PC Phase

6.4.6.2 TEMPO Results of Primary Analysis Based on ADAGIO Methodology

The analyses of TEMPO according to the ADAGIO methodology were post-hoc. It should be noted that the TEMPO study was not adequately powered for the 3 hypotheses.

Results for efficacy in the TEMPO study, based on ADAGIO analyses, are summarized in Table 28.

Table 28. TEMPO Reanalysis: Summary of Results Based on ADAGIO Hypotheses

Group	Estimate (95% CI)	Difference Between Groups (95% CI[a])	*p*-Value for Difference
Hypothesis #1: Comparison of Slopes from Week 14 to 26			
Placebo	0.218 (0.139, 0.297)	NA	NA
1 mg	0.133 (0.054, 0.212)	-0.085 (-0.197,0.026)	0.1342
2 mg	0.134 (0.053, 0.216)	-0.083 (-0.197,0.030)	0.1475
Hypothesis #2: Comparison of Change in UPDRS at Week 52			
2 mg delayed-start	2.814 (1.329, 4.299)	-0.696 (-2.753, 1.360)	0.5055
1 mg early-start	2.118 (0.659, 3.577)		
2 mg delayed-start	2.814 (1.329, 4.299)	-1.934 (-4.078, 0.209)	0.0768
2 mg early-start	0.880 (-0.667, 2.427)		
Hypothesis #3: Comparison of Slopes from Week 42 to 52			
2 mg delayed-start	0.172 (0.062, 0.282)	0.073 (-0.057, 0. 203)	NA
1 mg early-start	0.245 (0.136, 0.355)		
2 mg delayed-start	0.172 (0.062, 0.282)	-0.100 (-0.234, 0.033)	NA
2 mg early-start	0.072 (-0.044, 0.188)		

CI =confidence interval, ITT=intent-to-treat, NA=not applicable, UPDRS=Unified Parkinson's Disease Rating Scale.

a. 90% CI for Hypothesis #3.

Repeated Measures Mixed Linear using Unstructured Covariance Matrix; baseline UPDRS and center adjusted.

Hypothesis #1: In the TEMPO study, both the 1 mg and 2 mg doses showed slower deterioration compared to placebo during the PC phase; estimated effect sizes were numerically larger than those observed in ADAGIO, however, the 95% CI's contained zero (Table 28).

Hypothesis #2: Re-analysis of TEMPO patients included in the ACTE data set according to the ADAGIO study methods suggested a treatment effect of early over delayed treatment with rasagiline 2 mg, with LSM change from baseline to Week 52 of -1.934 UPDRS units (*P*=0.0768) (Table 28). Comparison of the 1 mg early-start group to the 2 mg delayed-start group (as there was no delayed-start 1 mg group) showed a treatment effect of about -0.7 UPDRS that did not exclude an effect of zero, similarly to the results of the original TEMPO analysis.

Hypothesis #3: The point estimate for the difference between the 2 mg early-start and delayed-start groups in the change in UPDRS per week was -0.1 (90% CI -0.234 to 0.033). The 90% CI upper limit of 0.033 did not exceeded the upper boundary of 0.15 UPDRS units/week, so non-inferiority was demonstrated for 2 mg early versus delayed start. The point estimate for the difference between the 1 mg early-start and 2 mg delayed-start groups in the change in UPDRS per week was 0.073 (90% CI -0.057 to 0.203). The upper limit of the CI exceeded the upper boundary of 0.15 UPDRS units/week, so non-inferiority was not demonstrated for 1mg early versus 2mg delayed start.

The estimates shown in TEMPO were consistent with those in ADAGIO.

6.4.7 Long-term Efficacy in TEMPO

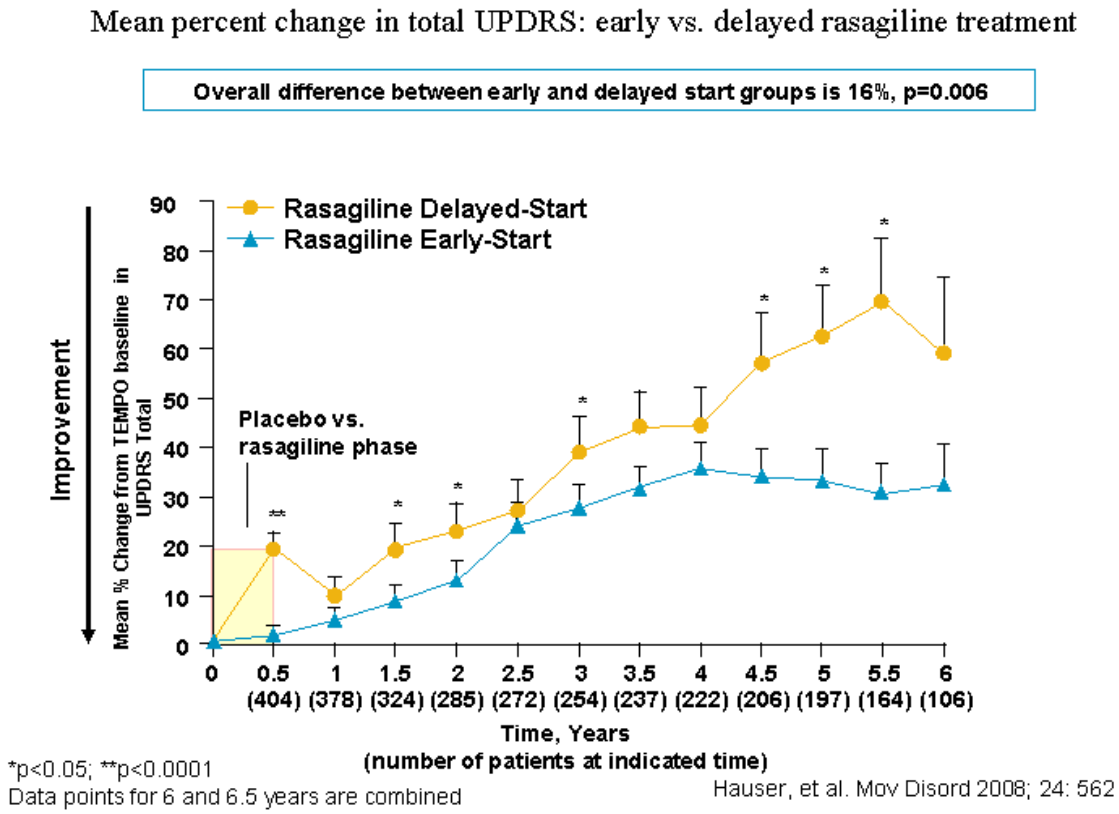
Long-term efficacy was assessed for patients who completed the 12-month TEMPO study (TVP-1012/232) and continued into its open-label extension study (TVP-1012/233). It should be noted that patients and investigators remained blinded to their original assignment throughout the extension study. The study was designed to follow the long-term efficacy, safety, and tolerability of rasagiline for PD. Of the 404 patients who started the TEMPO study, 306 patients participated in the open-label extension in which patients were treated with rasagiline as monotherapy, as well as an adjunct to other PD medications as needed, for up to 6.5 years with a mean ±SD of 3.6 ±2.1 years; of these, 177 patients received rasagiline for 5 years or more[79].

Post-hoc comparison of the UPDRS change from baseline to LOV for rasagiline early-start treatment vs. delayed-start was performed.

The findings should be interpreted with caution, due to the fact that their anti-PD treatment was not stable and the levodopa and dopamine agonists doses could be adjusted throughout the study as needed, and there were large numbers of drop outs. Also, the early-start group received numerically more levodopa dose equivalents on the day prior to each UPDRS visit (except at year 6). Although the difference in levodopa dose equivalents between the two groups was not differentiable from random noise for the entire cohort of 306 patients or for the 177 patients still in study at time of analysis, the possibility that a

non-significant difference affected clinical benefit could not be excluded. Nonetheless, the adjusted mean difference in the change from baseline in total UPDRS was 2.5 units (SE 1.1; *p*=0.021) or 16% (SE 5.7; *p*=0.006) in favor of the early-start versus delayed-start rasagiline group (Figure 11). Similar results were obtained for the group of 177 patients still in study at the time of analysis. Although the magnitude of difference between the early- and delayed-start groups varied over time, the early-start group was always numerically better as assessed by UPDRS scores. Less worsening (percent change) in total UPDRS scores was observed in the early-start group at time points between 0.5 and 5.5 years ($p < 0.05$ at all time points).

Figure 11. Mean Percent Change From Baseline in UPDRS Across Time



6.4.8 NHSS Model in TEMPO and ADAGIO

The NHSS model (see Appendix C) was applied to the data from the first phase (model 2) and to a dataset also including the early start data from the second phase since these patients did not change treatment (model 1). The NHSS is analogous to Hypothesis #1 in that it compares the slopes between treatment groups, but unlike the analysis of Hypothesis #1, the NHSS approach uses the relationship between the baseline UPDRS scores and the immediate (symptomatic) response to estimate the changing symptomatic effects. Thus the Natural History Estimate (NHE) adjusts the estimated slope difference between the treatment and placebo groups to account for these changing symptomatic effects; therefore, the main reason why simple slope separation does not necessarily indicate disease modification is taken into account.

The analyses of the ADAGIO trial under the NHSS model demonstrated a consistent, disease-modifying benefit with both the 1 mg and 2 mg doses of rasagiline (Table 29). Reduction in the rate of clinical decline compared with placebo, was 42.3% (model 1) and 22.4% (model 2) for the 1 mg dose group vs. placebo and 56.8% (model 1) and 55.1% (models 2) for the 2 mg dose group vs. placebo.

The results from analyses of the TEMPO trial were consistent in direction and magnitude with those from ADAGIO. The symptomatic effect that was estimated in both TEMPO and ADAGIO is generally slightly larger for patients with more severe disease, as evident from generally negative estimates of the cross-sectional association between baseline UPDRS score and the short-term symptomatic effect (i.e., the τ_1 parameter in the NHSS model – the average change in the magnitude of the symptomatic effect of treatment per one unit increase in baseline severity score). A negative value also indicates that the simple slope comparison (Hypothesis #1) would be expected to overestimate the disease modifying effect, and the delayed start estimate (Hypothesis #2) would be expected to underestimate the disease modifying effect. The NHE values provide evidence of consistent slowing of clinical progression.

Table 29. NHSS Model - Disease Modification Estimates

	Dose Group	Model	% Reduction in Decline from Placebo Rate	NHE (points per yr)	95% CI for NHE	
TEMPO						
Placebo vs. Early*	1 mg	1	53.9%	-5.89	-11.16	-0.61
First Phase Only	1 mg	2	38.4%	-4.19	-10.09	1.71
Placebo vs. Early	2 mg	1	58.2%	-6.16	-11.83	-0.49
First Phase Only	2 mg	2	36.0%	-3.81	-11.21	3.59
ADAGIO						
Placebo vs. Early	1 mg	1	42.3%	-3.13	-5.06	-1.19
First Phase	1 mg	2	22.4%	-1.66	-3.85	0.53
Placebo vs. Early	2 mg	1	56.8%	-4.25	-5.72	-2.77
First Phase	2 mg	2	55.1%	-4.11	-6.24	-1.98

CI=confidence interval, NHE=Natural History Estimate.

*Placebo vs. Early: a comparison of Placebo group vs. rasagiline which includes the second phase data for Early Start patients only.

6.4.9 Summary of Efficacy

TEMPO: a benefit of early treatment with rasagiline 2 mg was demonstrated in the 52-weeks analysis of the TEMPO study. A strict delayed-start analysis was not performed for the 1 mg dose due to lack of 1 mg delayed group; however, there was also evidence of a benefit when the early start 1 mg dose was compared with the delayed 2 mg dose[72].

ADAGIO: Analyses for 1 mg dose, showed a consistent advantage of early treatment with rasagiline 1 mg over delayed treatment. An effect was shown in the three hypotheses comprising the primary endpoint and this conclusion was confirmed in various sensitivity analyses accounting for the effect of missing observations in general, and especially for those related to early dropout or early transfer to active-treatment phase.

Hypothesis #1: A higher rate of deterioration in UPDRS scores during Weeks 12-36 of the PC phase was evident in both groups of 1 mg or 2 mg rasagiline-treated patients compared to placebo.

Hypothesis #2: No effect was demonstrated for early over delayed treatment with rasagiline 2 mg. Results are presented for the 1 mg early vs. delayed.

Hypothesis #2 in original SAP for which the study was powered: the results of the analyses of superiority in change from baseline across weeks 48-72 (active-treatment phase) in UPDRS were: a point estimate of -1. 408 with 95% CI [-2.50; -0.32] UPDRS units (p-value = 0.0115).

According to the pre-defined model in the Final SAP based on combined data set: the analysis conducted yielded a p-value of 0.0506 (point estimate [95% CI]: -1.425 [-2.85; 0.004]).

Alternative model – for separate data sets: the point estimate [95% CI] was: -1.680 [-3.15; -0.21] UPDRS units (p-value=0.025).

All the other sensitivity and supportive analyses for the 1 mg dose were consistent with the primary analyses.

Hypothesis #3: The rates of deterioration in UPDRS during the active-treatment phase were the same in the 1 mg delayed-start and early-start treatment groups and were similar for the 2 mg groups. The CIs for the difference for both dose levels were less than the non-inferiority margin, i.e. demonstrating non-converging slopes.

Additional data: When applying the ADAGIO methodology to TEMPO, post hoc, an advantage of early treatment was shown for the 2 mg. In the long-term TEMPO extension study, the data suggest that the benefits of early treatment with rasagiline might persist over time. The results of the NHSS model indicated a reduction in the rate of clinical progression in both TEMPO and ADAGIO studies andwith both doses of rasagiline.

7.0 Safety in TEMPO and ADAGIO

Table 30 shows the assessments that were conducted to evaluate the safety of rasagiline, including physical examinations, monitoring patients for adverse events, measurement of vital signs and laboratory values, and performing electrocardiograms (ECGs).

Table 30. Summary of Safety Assessments

	Placebo-Controlled Phase							Active-Treatment Phase					
Visit Week	**0**	**4**	**8**	**12/14[a]**	**20**	**24/26[a]**	**36**	**42/32[a]**	**48**	**54/42[a]**	**60/52[a]**	**66**	**72**
Physical Exam													
ADAGIO	√[b]						√						√
TEMPO	√[b]					√					√		
Adverse Events													
ADAGIO	√	√		√		√	√	√	√	√	√	√	√
TEMPO		√	√	√	√	√		√		√	√		
Laboratory Tests													
ADAGIO	√			√			√			√			√
TEMPO	√			√		√		√			√		
Vital Signs											√		
ADAGIO	√	√		√		√	√	√	√	√	√	√	√
TEMPO	√	√	√	√	√	√		√		√	√		
Electrocardiogram													
ADAGIO	√			√			√						√
TEMPO[c]													

a. ADAGIO/TEMPO.
b. Performed at Screening.
c. ECG data were interpreted by eResearch Technology (eRT), in both phases of ADAGIO but only for the PC phase of TEMPO. Therefore, analyses for the active-treatment phase were based on the ADAGIO study only.

This section summarizes safety experience observed in the TEMPO and ADAGIO studies. While the section focuses on the data sets of ADAGIO and TEMPO pooled for the PC Phase and the active-treatment phase, separate analyses were also conducted of each study to determine if the safety experience varied by study. Since the safety observations were generally similar across studies and this section, focuses on the pooled data of both studies.

7.1 Patients Included in the Integrated Analysis of Safety

7.1.1 Safety Population

All 1,578 patients who received at least one dose of study drug (placebo or rasagiline) in either the TEMPO (N=404) or ADAGIO (N=1174) study are included in the integrated analysis of safety. Table 31 summarizes the numbers of patients by study, phase (placebo control vs. active treatment), and treatment group.

Table 31. Distribution of TEMPO and ADAGIO Patients

PC Phase				
	Placebo	**Rasagiline 1 mg**	**Rasagiline 2 mg**	**Any Rasagiline Dose**
Pooled TEMPO+ADAGIO	731	422	425	847
TEMPO Study	138	134	132	266
ADAGIO Study	593	288	293	581

Active-treatment phase[a]						
	Rasagiline 1 mg		**Rasagiline 2 mg**		**Any Rasagiline Dose**	
	Delayed-Start	**Early-Start**	**Delayed-Start**	**Early-Start**	**Delayed-Start**	**Early-Start**
Pooled TEMPO+ADAGIO	270	397	407	397	677	794
TEMPO Study	not applicable	124	132	124	132	248
ADAGIO Study	270	273	275	273	545	546

a. Delayed-start patients received placebo during the placebo-controlled phase.

Demographic characteristics of study patients were generally similar between treatment groups in both studies (Table 4). TEMPO was conducted in North America (US and Canada) only, and ADAGIO was an international study conducted in North America, Europe, Israel, and Argentina. As dictated by the inclusion criteria, the patients in ADAGIO were at an earlier stage of their PD, as reflected by a shorter mean time from PD diagnosis and a lower mean baseline total UPDRS score (Table 6).

7.1.2 Extent of Exposure

In TEMPO, 398 PD patients were exposed to either rasagiline 1 or 2 mg, for a total of 305.02 patient-years. In ADAGIO, an additional 1,126 PD patients were exposed to either rasagiline 1 mg or 2 mg for a total of 1070.5 patient-years.

Exposure to study drug was similar across groups in each phase. In the pooled PC phase the mean ± SD exposure was 7.0±1.9 months in both the placebo and combined rasagiline groups. In the combined active-treatment phase, exposure was 7.2±2.0 months for the delayed-start group and 7.1±1.7 months for the early-start group. Table 32 summarizes exposure for the pooled PC phase.

Table 32. Pooled TEMPO + ADAGIO PC Phase: Exposure

	Rasagiline Doses			
Exposure	**Placebo N=731**	**Rasagiline 1 mg N=422**	**Rasagiline 2 mg N=425**	**Any Rasagiline Dose N=847**
Mean, days	212.3	215.1	212.3	213.7
Median, days	250	250	250	250
Range, days	1 - 287	5 - 285	7- 281	5 - 285

7.2 Adverse Events

The TEMPO study was conducted in North America (USA and Canada) only, while ADAGIO was an international study conducted in North America, Europe, Israel and Argentina. The proportion of subjects reporting AEs in TEMPO PC Phase was about 80% and in ADAGIO PC Phase about 67%. In the TEMPO PC Phase, the overall incidence of reported AEs was similar to that of North American subjects in the ADAGIO PC Phase. Pooling the studies yielded an overall incidence of about 71%. In the active-treatment phase of both studies AEs were reported at a similar rate (72% in TEMPO and 67% in ADAGIO). As the differences in reporting are relatively small, AEs are presented for the pooled-studies cohorts.

7.2.1 Commonly Reported Adverse Events in Pooled TEMPO+ADAGIO Cohorts

Overall in the pooled TEMPO+ADAGIO PC phases, AEs were reported for 70% of placebo subjects, 70.4% on rasagiline 1 mg and 73.2% on 2 mg. The most common[c] AEs in this cohort for the combined 1 mg and 2 mg group (any rasagiline dose) were headache, dizziness, fatigue, arthralgia and fall. Among them a dose response was evident only for dizziness as the dose increased from 0 mg (placebo) to 1 mg and 2 mg. Diarrhea and abdominal pain upper, were reported at a higher incidence in only one of the two doses.

In the pooled TEMPO+ADAGIO active-treatment phase a total of 66.6% AEs were reported in the delayed-start group of any rasagiline dose compared to 69.6% of the subjects in the early-start any rasagiline dose group. The largest difference in reporting AEs between early and delayed-start groups was shown in the 1 mg group (64.1% in delayed-start vs. 70.3% in early-start groups) while in the 2 mg group it was almost identical. The most common AEs in this cohort were: back pain, dizziness, arthralgia and nausea, while fall and nasopharyngitis had a higher incidence in the "delayed-start any dose" group. Headache was almost identically reported in both groups. Orthostatic hypotension occurred in 2.2% of the subjects in the delayed-start "any rasagiline dose" group and in 1.9% of the subjects in the early-start of the "any rasagiline dose" group, with a dose-response in the delayed-start groups. Nausea occurred more frequently in all early-start groups and a dose-response was evident within early-start groups.

[c] Numbers represent the number of patients per week. The larger number of patients in week 42 compared to week 36 was due to the early transfer of patients from the PC phase to Phase II.

7.2.2 Deaths, other Serious Adverse Events and other Adverse Events of Specific Clinical Importance

7.2.2.1 Deaths and other Serious Adverse Events

Three deaths were recorded in the ADAGIO database, two on rasagiline (one case of cerebral hemorrhage and one case of aortic aneurism rupture) assessed by the study investigator as unrelated to study drug, and one with metastatic rectal carcinoma who died 9 months after termination of placebo administration. No death was reported in TEMPO.

Serious AEs (SAEs) in the pooled TEMPO+ADAGIO PC Phase were recorded for 3.6% of the placebo-treated subjects and for 4.7% of rasagiline (1 mg or 2 mg) treated subjects. All individual SAEs (Preferred Term) were reported by less than 2% of the subjects in a treatment group in any of the PC cohorts; most SAEs in the PC cohorts were reported for one subject in each treatment group. SAEs reported by ≥ 0.5% of the subjects in the combined 1 mg or 2 mg group and higher than placebo by high level terms (HLTs) were: ischaemic coronary artery disorders and pain and discomfort Nec, each reported by 4 subjects (0.5%) vs. 2 subjects on placebo (0.3%).

SAEs in the pooled TEMPO+ADAGIO active-treatment phase were equally reported for delayed start of any dose (5.5%) or for early-start of any dose (5.7%). None of the individual SAEs [Preferred Terms (PTs)] was reported by 2% or more of the subjects in any of the Active cohorts.

7.2.2.2 Withdrawals due to an Adverse Event

Overall, TEMPO+ADAGIO PC Phase, AEs associated with premature termination were reported by 3.3% of rasagiline-treated subjects vs. 2.7% on placebo, with a higher incidence in the 1 mg group, but less than 2% in any individual dose group. The HLT of dyskinesias and movement disorders was recorded as leading to early termination (ET) in 3 rasagiline-treated subjects, all on 1 mg vs. one placebo subject. Few HLTs were recorded as leading to early termination for two rasagiline-treated subjects in either 1 mg or 2 mg dose group and higher than placebo.

A slightly higher incidence of early termination due to AEs was shown in the 2 mg groups for both delayed and early start groups for TEMPO+ADAGIO active-treatment phase. All AEs were recorded for one or two subjects only, in each of the treatment groups.

7.2.3 Other Adverse Events of Specific Clinical Importance

Some adverse events warranted special attention as requested by FDA.

Flu-like syndrome: For the TEMPO+ADAGIO PC Phase, 23.6% of subjects treated with any rasagiline dose and 20.8% of the subjects on placebo reported at least one of the symptoms associated with flu-like syndrome. Headache, arthralgia, cough and fatigue were reported by more than 2% of the subjects on any rasagiline dose and in higher incidence than placebo; however, the difference over placebo was less than 1%. These symptoms were the most common for the TEMPO+ADAGIO active-treatment phase as well.

Musculoskeletal syndrome: For the TEMPO+ADAGIO PC Phase, 19.4% of subjects treated with any rasagiline dose and 16.4% of the subjects on placebo reported at least one of the symptoms associated with musculoskeletal syndrome, where most reports were on rasagiline 2 mg (22.4%). Back pain, arthralgia, musculoskeletal pain, muscle spasm and pain in extremity were reported by more than 2% of the subjects on rasagiline and in higher incidence than placebo; however, the difference over placebo was less than 1%. All those symptoms were reported in higher incidence on 2 mg as compared to 1 mg. These symptoms were the most common for the TEMPO+ADAGIO active-treatment phase as well.

Fall: In the TEMPO+ADAGIO PC phase, in addition to the preferred term “fall” recorded for 4.0% of the rasagiline subjects (3.3% on 1 mg and 4.7% on 2 mg) and 3.8% of the placebo subjects other symptoms possibly suggestive of falls were explored. The incidence was similar between placebo and rasagiline groups. In the active-treatment phase of TEMPO+ADAGIO a higher incidence of fall as preferred term or in conjunction with symptoms possibly suggestive of falls was reported for the delayed-start groups. Within each of the delayed or early start groups a

higher incidence of falls was reported in the 2 mg groups. None of the AEs related to falls resulted in discontinuation from the studies.

Orthostatic hypotension/postural dizziness: Dose-response was manifested in TEMPO+ADAGIO PC Phase for AEs possibly suggestive of orthostatic hypotension/postural dizziness, where incidence of subjects reporting was 6.2% on 0 mg (placebo), 8.1% on 1 mg and 9.2% on 2 mg. In the TEMPO+ADAGIO active-treatment phase, the incidence of these AEs was higher in all early-start groups. In the delayed-start groups the incidence of such events was 2-fold in the 2 mg group compared to 1 mg, while it was slightly higher in the early-start 1 mg compared to early-start 2 mg.

Sleep attacks: Only one case of sleep attacks was reported; in the active-treatment phase of the ADAGIO study, in a subject on rasagiline 1 mg (early-start) with a history of sleep disorder, depression and thyroidectomy.

Rhabdomyolysis: No AEs of rhabdomyolysis were reported in any phase of the TEMPO or ADAGIO studies.

Malignant melanoma: Three cases of malignant melanoma were reported; two in TEMPO (both on rasagiline 2 mg) and one in ADAGIO (in the 1 mg early-start group; the latter was diagnosed at termination visit of the entire study.

Drug/Food interactions: In both phases of TEMPO and ADAGIO, as well as throughout the entire clinical program, there were no reports for any of the following AEs: tyramine-induced hypertensive crisis, serotonin syndrome in subjects using antidepressants concomitantly with rasagiline, or overdose. A few cases of these events were reported in the post-marketing period, all of which are reflected in the current labeling of Azilect®.

Elderly Population: Overall, a slightly higher incidence of AEs was reported in all treatment groups (placebo and rasagiline) for the older age group (≥65 years). AEs of clinical significance were reported at a low incidence in any group, but were more common among elderly subjects on rasagiline than on placebo in the TEMPO+ADAGIO PC cohort.

All AEs described in TEMPO and ADAGIO are already included in the current labeling.

7.3 Clinical Laboratory Evaluation

In the pooled TEMPO+ADAGIO PC Phase, potentially clinically significant (PCS) values were uncommon generally, and no value of PCS for any laboratory parameter in either study occurred in ≥ 2% more subjects in the rasagiline group compared to the placebo group. There was also no evidence of a dose-relationship for any laboratory change to a value of PCS in either study. With the possible exception of a greater increase in PCS cholesterol values in female subjects, neither age nor gender appeared to affect the incidences of laboratory PCS values, the incidence of which was not influenced by treatment with rasagiline.

In the pooled TEMPO+ADAGIO Phase, the low incidence of PCS values raises no clinical concern that treatment with rasagiline, whether started early or late, adversely influences biochemical or hematological parameters.

No rasagiline-treated subject was prematurely discontinued from the PC phases of the studies due to laboratory-related AEs and only one subject (rasagiline 2 mg early-start group) terminated the active-treatment phase of ADAGIO due to laboratory-related AE of "hepatic enzymes increased".

No laboratory data give rise to any clinical concern, or warrant any monitoring or special precaution.

7.4 Vital Signs

In the TEMPO+ADAGIO PC Phase, administration of rasagiline at doses of 1 mg or 2 mg was not associated with clinically relevant trends for changes in vital signs. Any differences that were observed were small, mainly in the 2 mg dose group.

Baseline-adjusted incidences of the various categories of orthostatic hypotension (OH): systolic blood pressure (SBP) OH ≥ 20 mmHg or ≥ 40 mmHg and diastolic BP (DBP) ≥ 10 mmHg or ≥

20 mmHg, were similar between either dose of rasagiline and placebo, with lower incidences in both groups at the final visit than at any visit. The one difference of ≥ +2% was in the incidence of SBP OH ≥ 20 mmHg for the comparison of rasagiline 2 mg with placebo at any visit during treatment (17.2% vs. 14.7% both for placebo and rasagiline 1 mg). The incidence of severe SBP OH (≥ 40 mmHg) in particular was more common in older subjects.

Systolic BP (SBP) increments (≥ 20 mmHg) in older subjects were slightly more common in rasagiline. This did not appear to be dose-related. No consistent age effect was apparent for Diastolic Blood Pressure (DBP). No gender effect was apparent on the incidence of any blood pressure (BP) changes

Only one subject in the PC Phase, in the rasagiline 2 mg group, prematurely discontinued the study due to the AE of hypertension. No subject was prematurely discontinued from the PC phases of the studies due to the AE of orthostatic hypotension.

Data from the active-treatment phases of the individual studies differed in a number of respects; however, there was no adverse trend overall for change in mean BP or pulse in the active-treatment phase of either study. For the pooled TEMPO+ADAGIO active-treatment phase, administration of rasagiline at doses of 1 mg or 2 mg was not associated with clinically relevant trends for changes in vital signs, whether administered early or with a delayed start.

There was no clear influence of the duration of dosing on changes in BP and no consistent dose relationship.

Changes in blood pressure, especially SBP changes, were more common in older subjects. The incidence of Systolic and Diastolic OH was also affected by age, being more common generally in the older age category. There was no consistent effect of gender on BP changes.

In the active-treatment phases, one subject, in the rasagiline 1 mg early start group, was a premature discontinuation due to hypertension, and one subject, in the rasagiline 2 mg delayed start group was a premature discontinuation, due to orthostatic hypotension.

7.5 Electrocardiogram Results

ECG data were centrally read in both phases of ADAGIO but only for the PC phase of TEMPO. Therefore, analyses for the active-treatment phase are based on the ADAGIO study only.

No ECG measurement gives rise to any clinical concern, or need for special precaution.

Relative to Baseline incidences and in comparison with placebo, there was no indication that treatment with rasagiline markedly prolongs QTc corrected by Bazett's formula (QTcB) or QTc corrected by Fridericia's formula (QTcF), nor was there clear evidence of a dose-relationship in marked QTc prolongation. No age or gender effect was apparent on QTc intervals ≥ 30 msec, nor for absolute values ≥ 450 msec.

Two subjects in the TEMPO+ADAGIO PC phases were prematurely discontinued from the study due to cardiac arrhythmias: one in the rasagiline 2 mg group for extrasystolic arrhythmia, and one in the rasagiline 1 mg group for atrial flutter.

In the ADAGIO active-treatment, duration of treatment (early start vs. delayed start) did not notably influence the ECG findings.

In a rasagiline TQT study (TVP-1012/121), it was concluded that rasagiline had no effects on heart rate, PR and QRS interval duration or notable changes in cardiac morphology. The analysis of data including a careful pharmacodynamic-pharmacokinetic (PK) analysis showed that rasagiline had no effects on cardiac re-polarization. There does not appear to be a rasagiline-related effect on ECG.

7.6 Safety Summary

The overall AE profile of the exhibited in both phases of the TEMPO and ADAGIO studies in monotherapy of PD patients is similar to that currently included in the labeling. Pooling the AE

data from the ADAGIO study increased the precision of adverse reaction rates and provided a more clinically useful representation of rasagiline's favorable adverse reaction profile.

The addition of the larger and longer ADAGIO study did not result in a notable increase in dopaminergic or cardiovascular AEs and no cumulative adverse effect was seen in long-term treatment. No change was seen in vital signs, ECG or biochemistry parameters. The additional data also do not indicate rasagiline related risk with regard to hematology laboratory abnormalities. Although rasagiline 1 and 2 mg/day was administered without dietary tyramine restriction it was not associated with increased risk for tyramine reaction.

Overall, the increased drug exposure has not substantially altered the documented satisfactory safety profile of rasagiline.

8.0 Summary of Post-Marketing Surveillance

Since the approval of Azilect® in 2005 until the end of June 2011 a total of about 500,000 patient-years of worldwide exposure to Azilect® have been accumulated, not including clinical trials. Cumulatively there are 950 medically confirmed cases of AEs in TEVA's Pharmacovigilance data base.

Review of the cumulative post-marketing safety data done in December 2008 initiated several modifications to the Company Core Data Sheet (CCDS) that were done during 2009. These changes reflect the possible development of:

Serotonin syndrome in patients treated with Azilect® concomitantly with antidepressants/SNRIs

Elevated blood pressure

Symptomatic overdose

Consequently, the US label, the Canadian Product Monograph, and the Summary of Product Characteristics (SPC) were revised to include these issues.

A cumulative review of the post-marketing safety data through December 2010 (the cut-off date for this report) identified no new safety concerns. No frequency increase in AE reporting associated with Azilect® was identified. No new significant drug abuse or misuse, experiences during pregnancy or lactation, experience in special patient groups, or effects of long-term treatment was brought to the attention of Teva.

Skin Exams and Melanoma Risk: Based on global marketing estimates, approximately 166,233 PD patients have been exposed to Azilect® resulting in an approximate of 399,120 patient-years of exposure to rasagiline in the post-marketing period worldwide. Three medically confirmed cases of malignant melanoma which occurred during Azilect® treatment were reported to TEVA Pharmacovigilance. One case was reported in a PD male patient eight months on Azilect® treatment. This patient had risk factors such as blue eyes and sun sensitivity. The second case is a literature case concerning an elderly PD patient treated concomitantly with Azilect® and other PD medication. Melanoma in-situ was diagnosed after 1.5 years of the mentioned PD treatment in a facial lesion that appeared half a year after the PD treatment initiation. In the third case, melanoma was diagnosed 3 months after Azilect® initiation in a nevus located on the toe of a blond haired Caucasian man. This nevus was known for a year prior to Azilect® initiation but was never evaluated before.

Interaction between Rasagiline and Antidepressants: A total of 13 non-fatal, medically confirmed reports of serotonin syndrome associated with agitation, confusion, rigidity, pyrexia and myoclonus had been

reported to Teva in patients using Azilect® and antidepressants concomitantly or in Azilect® overdose as already reflected in the CCDS.

Possible Tyramine-Induced Hypertensive Reaction: Seven medically confirmed cases of tyramine reaction were reported. In none of these cases did the systolic or diastolic blood pressure reach 240 and 130 mm Hg, respectively. There was no reported end organ damage as a result of the increase in the blood pressure. These cases are already included in Section 5.4 of the labeling.

Overdose, Pregnancy and Lactation, and Other: A few cases of Azilect® overdose and misuse requiring no special intervention except for drug discontinuation were reported. No new significant drug abuse or misuse, experiences during pregnancy or lactation, experience in special patient groups or effects of long term treatment was brought to the attention of Teva.

9.0 Benefit-Risk Considerations

9.1 Unmet Medical Need

Idiopathic PD has an annual incidence in developed countries of 12-20 cases per 100,000 population[44] and is second only to Alzheimer's disease (AD) as the most common neurodegenerative disorder. Currently treatments provide symptomatic control for most PD patients in the early to intermediate phases of their disease when motor impairments predominate[47.] As disease progresses, symptoms reflecting development of motor complications, impairments such as freezing, postural instability, autonomic dysfunction and dementia occur which are not satisfactorily controlled with symptomatic treatment. Eventually severe impairment and disability occur[47,80]. The progressive nature of PD reflects underlying multisystem neuronal degeneration of PD that characterizes the natural history of the disease. Currently, there is no approved treatment that slow the progression of PD with the absence of effective new treatment represented a substantial public health need[3].

Over the past 20 years, numerous clinical trials evaluated various compounds as putative neuroprotective agents in PD[49,50.] but none of them could be identified as disease modifying agent. Since there are no efficacy endpoints in PD that assess the underlying disease state, disease modification study designs must use disease symptom scores to separate symptomatic effects from disease modifying effects[66,]. Most compounds studied to date are also symptomatic agents[65,81].

Teva, selected a two-period delayed-start design to differentiate symptomatic effects from a slowing of disease progression. In the placebo-controlled phase, patients are randomized to active treatment or placebo while in the active-treatment phase, patients in both groups are placed on the active treatment. Patients that have a delay in receiving active treatment serve as the control for patients that received early treatment. If at the end of the active-treatment phase there is no difference in the symptom scores, then the patients that had a delay in treatment have caught up with those that had early treatment, indicating that the effect was only symptomatic. In contrast, a slowing of disease progression is affirmed if the early treatment group remains better

off than the delayed treatment group at the end of the active-treatment phase. The underlying assumption in this comparison is that the symptomatic effect occurs early in treatment[66].

9.2 Summary of the Evidence that Rasagiline Slows Disease Progression

In the two independent double-blind studies, ADAGIO and TEMPO, rasagiline produced a beneficial slowing of disease progression for early treatment compared to delayed treatment. TEMPO affirmed a benefit for early treatment with 2 mg with support for the 1 mg dose[72]. ADAGIO affirmed a benefit of early treatment for 1 mg. Additional supportive analyses in ADAGIO found robust support for 1 mg. In ADAGIO, early treatment with the 2mg dose did not find any difference with delayed treatment at the end of the trial despite demonstrating a difference in the rate of progression in the placebo-controlled phase of the trial. Collectively, TEMPO and ADAGIO provide independent substantiation that early treatment with rasagiline slows clinical progression as measured by UPDRS scores.

9.2.1 Interpretation of the 2 mg Results in ADAGIO

The main concern with the interpretation of the ADAGIO results is the failure of the 2 mg to reject Hypothesis #2, especially since the TEMPO showed a benefit at this dose. Discussed below are several possible explanations.

First, the pharmacokinetic and pharmacodynamic profile of rasagiline was assessed in order to try and understand the different results of the two doses in ADAGIO. The parent drug rasagiline has a very short half life (mean = 3 hours) in human blood. Its metabolite, aminoindan, has also demonstrated beneficial effects in experimental models, and has a longer half life of 11 hours. Based on a PK study in healthy volunteers, rasagiline in the range of 1-6 mg demonstrated a more then proportional increase in AUC, while Cmax was dose proportional. However, it is well known that the pharmacodynamic effect leading to MAO-B inhibition lasts much longer than this. Less is known regarding other activities of the molecule, although in experimental models it appears that the neuroprotective effects of rasagiline are not solely dependent on MAO-B

inhibition. Therefore, it is not clear if the pharmacokinetic profile of the drug is fully predictive of the pharmacological effect.

In terms of pharmacological effect, in a 10 week dose range finding the active-treatment phase monotherapy study in early Parkinson's disease patients, the 1 mg dose had less effect on UPDRS than the 2 or 4 mg. However, this difference was not seen between 1 and 2 mg doses in the placebo-controlled phases of the larger TEMPO and ADAGIO studies. Taken together, there is no solid basis to expect different pharmacological effects in patients after chronic dosing with 1 or 2 mg rasagiline per day.

Another possible explanation for the failure of the 2 mg dose in ADAGIO on Hypothesis #2 could be the difference between populations in each group especially in the active-treatment phase caused by dropout and, in particular, the differential early transfer to the active-treatment phase from the early versus delayed treatment groups. Approximately twice as many subjects transferred early from the delayed-start groups as compared to the early-start groups (20% as compared to 10%). Although similar for the two doses, the larger number of early transfers in the delayed start arms contributed to the different populations between the groups at the start of the active-treatment phase. These more severe patients would presumably have declined more had they remained in the trial for the full 72 weeks. While this does not explain the difference between the two doses, it did make it more challenging for either dose to demonstrate a benefit of early treatment at the end of the trial (Hypothesis #2).

An additional explanation for the failure of the 2 mg dose relates to the UPDRS “floor effect”. With the mild PD symptoms of the population in ADAGIO (mean baseline UPDRS, 20 points) a “floor effect” can occur with a symptomatic scale like the UPDRS, when the less severe symptoms are not captured by the scale. Thus, in mild patients, there is a lower limit or “floor” to the treatment response that can be detected. As patients advance, as in the second phase of ADAGIO, the response is greater because of the higher UPDRS scores that allow for more room for detection. Thus, beneficial effect from early treatment with 2mg might be washed out by the size of the larger symptomatic effect observed when placebo is switched to 2 mg. ADAGIO patients were amongst the mildest group of PD patients ever studied, with milder and shorter

disease duration than patients in the TEMPO study.. This might account for why there was a difference in the two studies.

If this floor effect exists, one may expect an effect on clinical progression to be demonstrable in a subset of patients with more advanced disease. Indeed, a post-hoc analysis using the subset of patients in ADAGIO with the highest baseline UPDRS scores demonstrated a pronounced benefit (-3.63) of early 2 mg vs. delayed 2 mg treatment on the change from baseline to Week 72 in patients with the baseline UPDRS scores (>25.5).

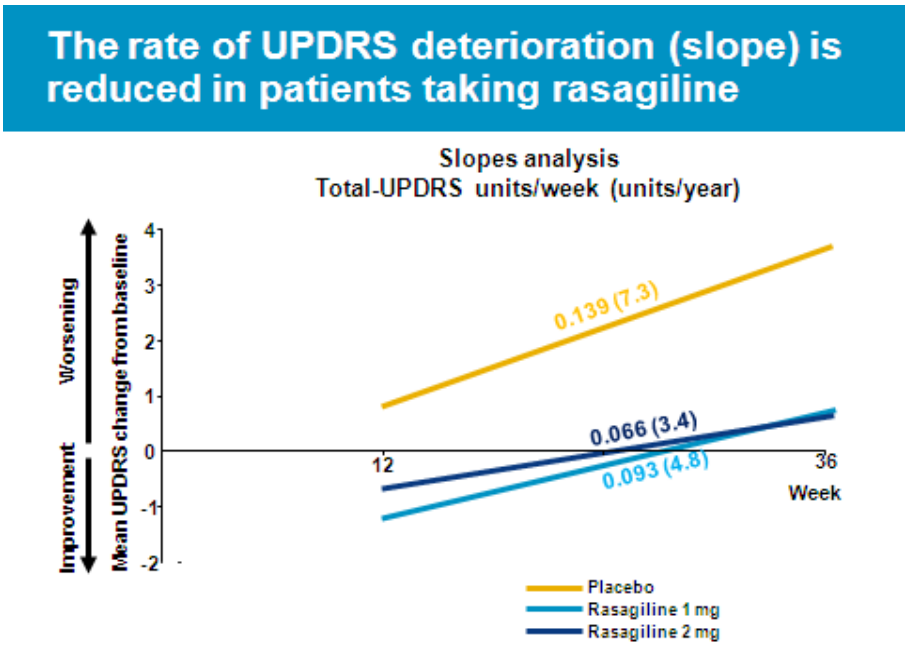
Other studies have shown strong evidence of an interaction between treatment and disease severity, such that symptomatic effects of drug treatment were more effective for subjects with more severe disease at baseline[82-84]. Similar findings were shown in both early and advanced patients. Thus, analysis of more advanced PD patients may allow for greater detection of overall effects using clinical scales such as the UPDRS, and therefore better separation between symptomatic and disease-modifying effects.

9.3 Clinical Significance of Rasagiline's Slowing of Disease Progression

In ADAGIO, over weeks 12-36, after it was assumed that the full symptomatic effect had taken place, the rate of worsening in the UPDRS was 0.093 UPDRS units/week or 4.8 UPDRS units/year for 1 mg and 0.066 UPDRS units/week or 3.4 UPDRS units/year for 2 mg compared to a worsening of 0.139 UPDRS units/week or 7.3 UPDRS units/year observed with placebo[d] (Figure 12). Thus, differences versus placebo are 2.5 UPDRS units/year for the 1 mg dose and 3.9 UPDRS units/year for the 2 mg dose.

[d] Studies in PD using comparable patient populations to ADAGIO have reported annualized deterioration rates for placebo patients of 8-12 UPDRS units/year. When ADAGIO data is calculated in a similar fashion, the annualized deterioration rate is 6 UPDRS units/year for placebo patients[51,54,72,85-87].

Figure 12. Rate of UPDRS Deterioration in the PC of ADAGIO

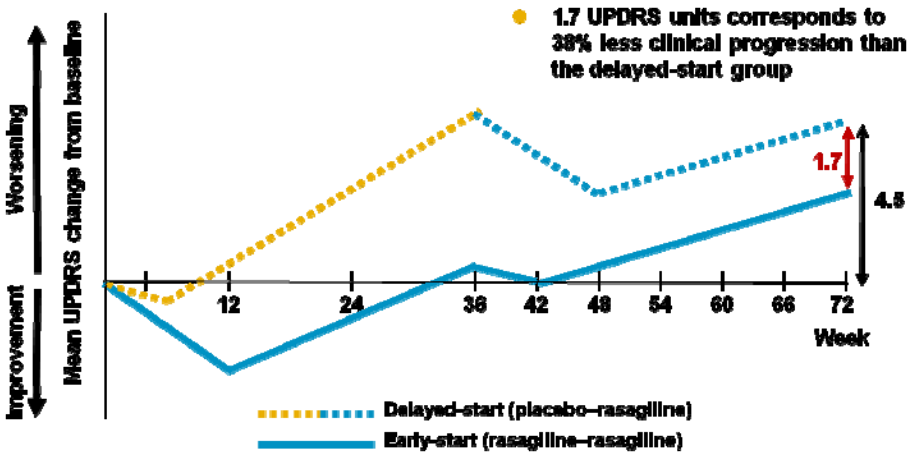


At Week 72 in ADAGIO, the difference between the early and delay treatment groups averaged approximately 1.7 UPDRS units across the many different analyses. One challenge to interpreting the clinical significance of the slowing of progression observed in ADAGIO is the tendency to compare the effect size to that typically seen in symptomatic effect trials. For example, comparing the 72 week finding of 1.7, to those suggested to affirm a clinically meaningful effect for symptom relief (reports of 1.5, 3.5, or 8 UPDRS units[88-90]). Such comparisons may be misleading since a delayed-start design assesses a clinical benefit separate from that which is symptomatic. Furthermore, a large difference in UPDRS between early- and delayed-start groups may not be expected in a delayed-start study since the difference in drug exposure between groups is not large (i.e. 36 weeks for ADAGIO). The ADAGIO data, in particular, must also be evaluated keeping in mind that it enrolled a relatively mild patient population (mean Total-UPDRS at baseline 20.4) since, in general, it is more difficult to detect improvement in patients with lower UPDRS scores[83].

The clinical significance of treatment effect of 1.7 UPDRS units was assessed in several ways as follows. For illustrative purposes, the estimated changes from baseline in UPDRS from the analyses of the separate datasets are used. Results are consistent using other analysis approaches.

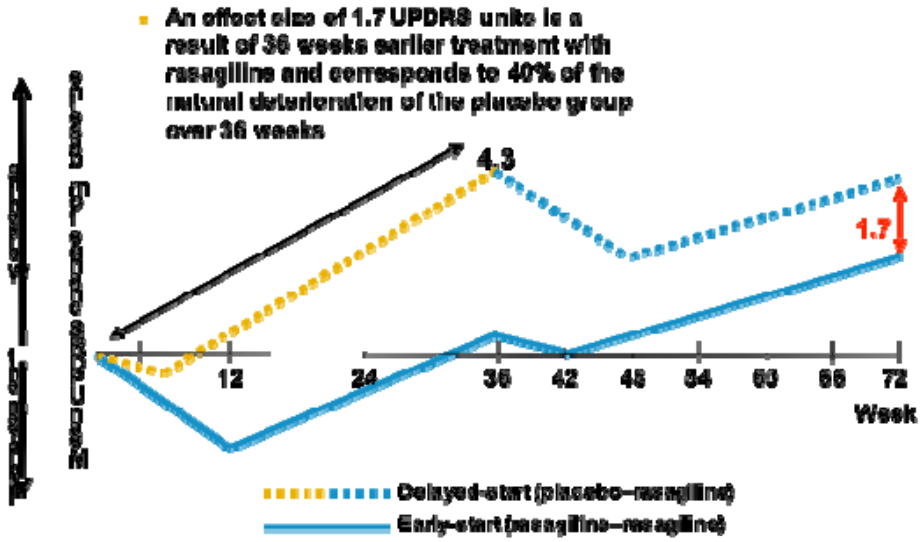
1) Patients in the 1 mg delayed-start group worsened by 4.5 UPDRS over the course of the study. The 1.7 UPDRS units difference then translates to a 38% reduction in clinical progression ([1.7/4.5] x 100% = 38%); Figure 13. This benefit is derived from only 9 months of earlier rasagiline treatment, as both groups received rasagiline in the active-treatment phase of the study.

Figure 13. UPDRS Deterioration: Delayed vs. Early-Start Groups at Week 72 in ADAGIO



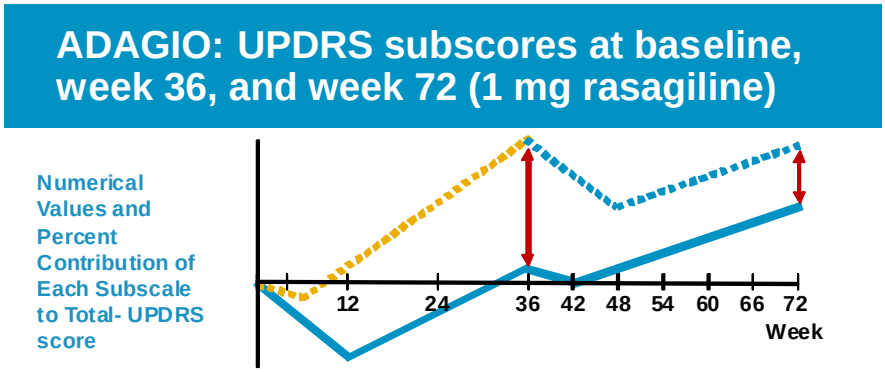
2) The deterioration in Total-UPDRS score for placebo patients in the ADAGIO study was 4.3 units at 36 weeks (Figure 14), which, as mentioned above, was less than that of other large studies in similar PD populations. Since the observed effect size of 1.7 units is due to a difference of 36 weeks of treatment with rasagiline (between early- and delayed-start 1mg groups), it represents a 40% reduction in the natural deterioration of the ADAGIO cohort ([1.7/4.3] x 100% = 40%).

Figure 14. Change in UPDRS: Delayed vs. Early-Start Groups – Weeks 72 vs. 36 in ADAGIO



3) When looking at the contribution of the UPDRS subscales to the different effects of rasagiline, as recently published in Lancet Neurology[78], one can gain further insight into the relevance for the PD patient. As seen in Figure 15, at Week 36 there was a significant difference in change from baseline between placebo and rasagiline groups in all three UPDRS subscales. At Week 72 there was a significant difference in the change from baseline between the early and delayed-start groups in the ADL subscale. Moreover, the ADL component contributed 41% to the benefit seen at Week 72 (effect on slowing clinical progression), compared to a 29% contribution to the benefit seen vs. placebo at Week 36 (symptomatic effect plus effects on slowing clinical progression).

Figure 15. ADAGIO: UPDRS Subscores at Baseline, Week 36, and Week 72 (1 mg Rasagiline Group)



	Baseline scores			Treatment effect at Week 36 Rasagiline vs. placebo			Treatment effect at Week 72 Early-start vs. delayed-start		
Mentation	1.0	1.3	(5%)	-0.22	0.08*	(7%)	-0.12	0.10	(8%)
ADL	5.1	2.8	(25%)	-0.86	0.18**	(29%)	-0.62	0.29*	(41%)
Motor	14.5	6.3	(70%)	-1.88	0.35**	(64%)	-0.76	0.51	(51%)

*p<0.05; **p<0.0001

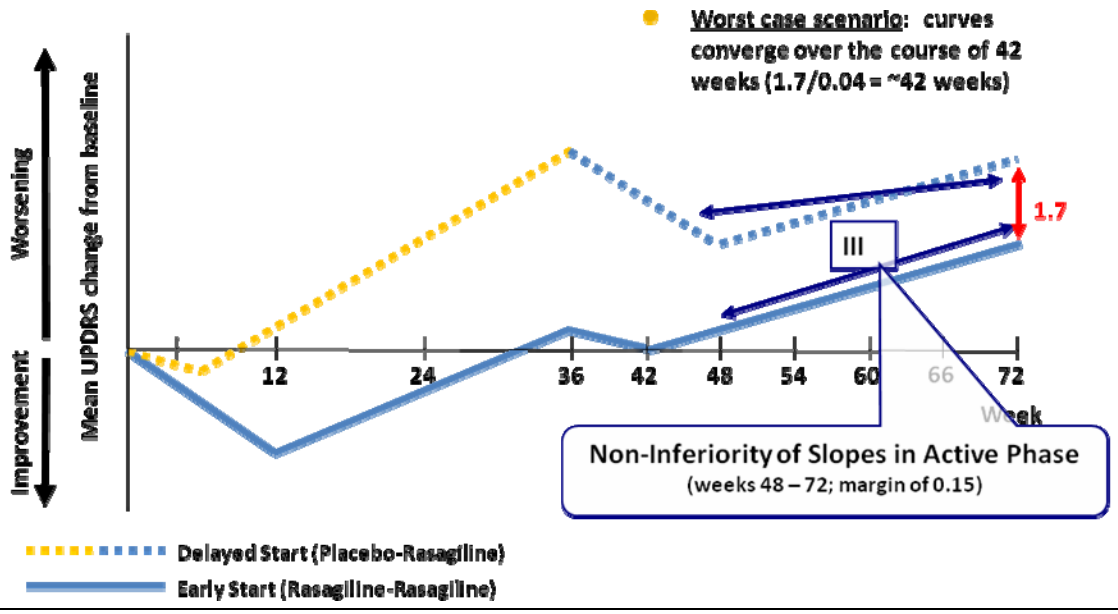
The significant contribution of the ADL subscore to the 72-week treatment effect is consistent with the developing hypothesis that patient-oriented functional outcomes are more appropriate than motor outcomes in assessing disease progression in PD[76,77]. The concept of ADL as a more stable marker of disease progression is attractive in its simplicity and relevance to patients' function[91]. UPDRS ADL scores are derived from the patient's report of function over the past week, and thus might be less sensitive to short-term variability driven by environment or investigators. ADL subscores might also be more sensitive to subtle functional changes (eg, in hygiene, dressing, and eating) that affect the patient but are not necessarily captured by motor subscores in the office assessment.

The non-inferiority analysis of Hypothesis #3 also provides reassuring interpretation of the ADAGIO results. A non-inferiority margin is a small amount that is allowed to be 'given away' when testing whether one result is better or worse than another. In fact the actual difference in slopes between early- and delayed-start 1mg groups was 0.0 units per week, which means the disease progression curves were actually parallel. The confidence intervals for the calculated difference of 0.0 ranged across the different analyses but had upper limits that were at most about 0.04. This value can inform us of the rate at which the slopes might be converging in a realistic worse case scenario or diverging (a negative value; best case scenario).

For the observed difference of 1.7 UPDRS units, and the observed upper CI for the slope (0.04 UPDRS units/week), it would take ~42 weeks for the delayed-start group to 'catch up' to the early-start group (1.7/0.04 = ~42 weeks; Figure 16).

On the other hand, for the observed difference of 1.7 UPDRS units, and the observed lower CI for the slope (-0.04 UPDRS units/week), the early- and delayed-start groups would continue to diverge over time.

Figure 16. Rate of UPDRS Deterioration in the Active-treatment phase of ADAGIO



9.4 Summary of Risks

The overall AE profile exhibited in both phases of the TEMPO and ADAGIO studies in monotherapy of PD patients is similar to that currently included in the labeling. Pooling the AE data from the ADAGIO study increased the precision of adverse reaction rates and further supported rasagiline's favorable adverse reaction profile.

The addition of the bigger and longer ADAGIO study did not result in a notable increase in dopaminergic or cardiovascular AEs and no cumulative adverse effect was seen in long-term treatment. No clinically significant change was seen in vital signs, ECG or biochemistry parameters. The additional data also do not indicate rasagiline related risk with regard to hematology laboratory abnormalities. Although rasagiline 1 and 2 mg/day was administered without dietary tyramine restriction it was not associated with increased risk for tyramine reaction. Approximately one third of patients took anti-depressants and no interactions were reported. Only one patient had a melanoma (in the 1mg group). It is noteworthy that 3 patients were detected to have melanoma at screening and did not participate in the study.

Overall, the drug is well tolerated and has a favorable safety profile. Results of the ADAGIO study do not alter the documented satisfactory safety profile of rasagiline.

9.5 Conclusions

Early treatment with rasagiline in two double-blind studies (TEMPO and ADAGIO) provided independent substantiation that rasagiline slows clinical progression of the PD. Rates of decline diverged in the placebo-controlled phases after the establishment of symptomatic benefits consistent with what would be expected from a treatment that affects the rate of clinical progression. At the end of the trials, early treatment provided benefits that could not be achieved with delayed treatment (~38% improvement) even though all subjects had been on the same treatment throughout the full duration of the active-treatment phase. Analyses of slopes for the active-treatment phase of the study demonstrated that the early and delayed treatment groups

were not rapidly converging, affirming an effect on disease progression and that the beneficial effects had endured for at least 12-18 months. These benefits cannot be readily explained by an effect on symptoms alone and are consistent with rasagiline slowing the rate of PD clinical progression as determined by the change in UPDRS score.

Both doses of rasagiline were well tolerated and associated with good safety profiles in the TEMPO and ADAGIO studies. Motor complications, impulse control disorders, hepatic dysfunction, and diarrhea, as seen with other dopaminergic agents, were not associated with rasagiline.

In conclusion, PD is an inexorably progressive disorder that ultimately leads to intolerable disability despite currently available medical and surgical therapies. There are no approved treatments shown to slow PD progression. The totality of the evidence with Azilect® affirms a clinically significant slowing of PD progression and Azilect's favorable safety profile remains unchanged. Thus, Teva believes there is substantial evidence for the indication presented in the supplemental NDA for Azilect® 1 mg to be approved.

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11.0 Appendices

Appendix A. Unified Parkinson's Disease Rating Scale (UPDRS, Version 3)

PART I. MENTATION, BEHAVIOR AND MOOD (RATE ITEMS 1 TO 4 BY INTERVIEW)

When completing this section, indicate the patient's best level of function during the past week.

1. <u>Intellectual impairment:</u>

0 = None

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (due to dementia or drug intoxication):

0 = None

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression:

0 = Not present.

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

2 = Sustained depression (1 week or more).

3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).

4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative:

0 = Normal.

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (non-routine) activities.

3 = Loss of initiative or disinterest in day-to-day (routine) activities.

4 = Withdrawn, complete loss of motivation.

PART II ACTIVITIES OF DAILY LIVING

5. Speech:

0 = Normal

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation:

0 = Normal

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing:

0 = Normal.

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrostomy feeding.

8. Handwriting:

0 = Normal

1 = Slightly slow and small.

2 = Moderately slow or small; all words are legible.

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

9. Cutting food and handling utensils:

0 = Normal

1 = Somewhat slow and clumsy, but no help needed.

2 = Can cut most foods, although clumsy and slow; some help needed.

3 = Food must be cut by someone, but can still feed slowly.

4 = Needs to be fed.

10. Dressing:

0 = Normal

1 = Somewhat slow, but no help needed.

2 = Occasional assistance with buttoning, getting arms in sleeves.

3 = Considerable help required; but can do some things alone.

4 = Helpless.

11. Hygiene:

0 = Normal

1 = Somewhat slow, but no help needed.

2 = Needs help to shower or bathe; or very slow in hygienic care.

3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.

4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bedclothes:

0 = Normal

1 = Somewhat slow and clumsy, but no help needed.

2 = Can turn alone or adjust sheets, but with great difficulty.

3 = Can initiate, but not turn or adjust sheets alone.

4 = Helpless.

13. Falling (unrelated to freezing):

0 = None

1 = Rare falling.

2 = Occasionally falls, less than once per day.

3 = Falls an average of once daily.

4 = Falls more than once daily.

14. Freezing when walking:

0 = None

1 = Rare freezing when walking; may have start-hesitation.

2 = Occasional freezing when walking.

3 = Frequent freezing. Occasionally falls from freezing.

4 = Frequent falls from freezing.

15. Walking:

0 = Normal

1 = Mild difficulty. May not swing arms or may tend to drag leg.

2 = Moderate difficulty, but requires little or no assistance.

3 = Severe disturbance of walking, requiring assistance.

4 = Cannot walk at all, even with assistance.

16. Tremor:

0 = Absent

1 = Slight and infrequently present.

2 = Moderate; bothersome to patient.

3 = Severe; interferes with many activities.

4 = Marked; interferes with most activities.

17. Sensory complaints related to Parkinsonism:

0 = None

1 = Occasionally has numbness, tingling, or mild aching.

2 = Frequently has numbness, tingling, or aching, not distressing.

3 = Frequent painful sensations.

4 = Excruciating pain.

PART III MOTOR EXAMINATION

18. Speech:

0 = Normal

1 = Slight loss of expression, diction, and/or volume.

2 = Monotone, slurred but understandable; moderately impaired.

3 = Marked impairment, difficult to understand.

4 = Unintelligible.

19. Facial expression:

0 = Normal

1 = Minimal hypomimia, could be normal "Poker Face".

2 = Slight but definitely abnormal diminution of facial expression.

3 = Moderate hypomimia; lips parted some of the time.

4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (F = Face, LH = Left Hand, RH = Right Hand, LF = Left Foot, RF = Right Foot):

0 = Absent

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent, or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present all of the time.

4 = Marked in amplitude and present most of the time.

21. Action or postural tremor of hands:

0 = Absent

1 = Slight; present with action.

2 = Moderate in amplitude, present with action.

3 = Moderate in amplitude, with posture holding as well as action.

4 = Marked in amplitude, interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.):

LUE = Left Upper Extremities

RUE = Right Upper Extremities

LLE = Left Lower Extremities

RLE = Right Lower Extremities

0 = Absent

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

23. Finger taps (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.) (Left and Right hand):

0 = Normal

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

24. Hand movements (Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.) (Left and Right hand):

0 = Normal

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

25. Rapid alternating movements of hands (Pronation - supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.):

0 = Normal

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

26. Leg agility (with knee bent, patient taps foot on ground in rapid succession.) (left and right leg):

0 = Normal

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

27. Arising from chair (Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.):

0 = Normal

1 = Slow; or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture:

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait:

0 = Normal

1 = Walks slowly, may shuffle with short steps, but no festination or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural stability (Response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.):

0 = Normal

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body bradykinesia and hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude and poverty of movement in general.):

0 = None

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.

PART IV COMPLICATIONS OF THERAPY (IN THE PAST WEEK)

A. Dyskinesias

32. **Duration:** What proportion of the waking day are the dyskinesias present? (historical information):

0 = None

1 = 1-25% of day

2 = 26-50% of day

3 = 51-75% of day

4 = 76-100% of day

33. **Disability:** How disabling are the dyskinesias? (historical information; may be modified by office examination):

0 = Not disabling

1 = Mildly disabling

2 = Moderately disabling

3 = Severely disabling

4 = Completely disabling

34. **Painful dyskinesias**. How painful are the dyskinesias?

0 = No painful dyskinesias

1 = Slightly

2 = Moderately

3 = Severely

4 = Markedly

35 Presence of early morning dystonia (historical information):

(0 = No, 1 = Yes)

B. Clinical Fluctuations

36. Are any "off" periods predictable as to timing after a dose of medication?

(0 = No, 1 = Yes)

37. Are any "off" periods unpredictable as to timing after a dose of medication?
(0 = No, 1 = Yes)

38. Do any "off" periods come on suddenly (e.g., within a few seconds)?
(0 = No, 1 = Yes)

39. What proportion of the waking day is the subject "off," on average?

0 = None

1 = 1-25% of day

2 = 26-50% of day

3 = 51-75% of day

4 = 76-100% of day

C. Other Complications

40. Does the subject have anorexia, nausea, or vomiting?

(0 = No, 1 = Yes)

41. Does the subject have any sleep disturbances? (e.g., insomnia or hypersomnolence)?

(0 = No, 1 = Yes)

42. Does the subject have symptomatic orthostasis?

(0 = No, 1 = Yes)

Appendix B. Additional TEMPO and ADAGIO Tables

Table B1. TEMPO: Reasons for Patient Premature Termination during Placebo-Controlled Phase by the Need for Additional anti-PD Therapy

Need for Additional Therapy	Termination Reason	1 mg		2 mg		Placebo		All	
		N	%	N	%	N	%	N	%
No	Normal completion	111	93.3	105	95.5	112	97.4	328	95.3
	AE	5	4.2	1	0.9	1	0.9	7	2.0
	Failed to return	1	0.8	.	.	.	.	1	0.3
	Subject request	2	1.7	2	1.8	2	1.7	6	1.7
	Unsatisfactory response	.	.	1	0.9	.	.	1	0.3
	Other	.	.	1	0.9	.	.	1	0.3
	All	119	88.8	110	83.3	115	83.3	344	85.1
Yes	Normal completion	14	93.3	19	86.4	21	91.3	54	90.0
	AE	.	.	1	4.5	.	.	1	1.7
	Subject request	.	.	.	.	1	4.3	1	1.7
	Unsatisfactory response	.	.	1	4.5	1	4.3	2	3.3
	Protocol violation	.	.	1	4.5	.	.	1	1.7
	Other	1	6.7	.	.	.	.	1	1.7
	All	15	11.2	22	16.7	23	16.7	60	14.9
All	Normal Completion	125	93.3	124	93.9	133	96.4	382	94.6
	AE	5	3.7	2	1.5	1	0.7	8	2.0
	Failed to return	1	0.7	.	.	.	.	1	0.2
	Subject request	2	1.5	2	1.5	3	2.2	7	1.7
	Unsatisfactory response	.	.	2	1.5	1	0.7	3	0.7
	Protocol violation	.	.	1	0.8	.	.	1	0.2
	Other	1	0.7	1	0.8	.	.	2	0.5
	All	134	100.0	132	100.0	138	100.0	404	100.0

Table B2. TEMPO: Reasons for Patient Premature Termination during Active-Treatment Phase

TEMPO	1 mg		2 mg		Placebo/2 mg		All	
	N	%	N	%	N	%	N	%
All	124	100.0	124	100.0	132	100.0	380	100.0
Termination Reason:								
Normal completion	120	96.8	118	95.2	122	92.4	360	94.7
AE	.	.	2	1.6	3	2.3	5	1.3
Subject request	2	1.6	3	2.4	4	3.0	9	2.4
Unsatisfactory response	.	.	.	.	1	0.8	1	0.3
Other	2	1.6	1	0.8	2	1.5	5	1.3

Table B3. ADAGIO: Reasons for Patient Premature Termination During Placebo-Controlled Phase

ADAGIO	1 mg Delayed Start (N=298)		1 mg Early Start (N=288)		2 mg Delayed Start (N=295)		2 mg Early Start (N=293)		All	
Reason for Premature Discontinuation	N	%	N	%	N	%	N	%	N	%
Received double-blind medication	298	100.0	288	100.0	295	100.0	293	100.0	1174	100.0
Subject withdrew consent	9	3.0	3	1.0	6	2.0	3	1.0	21	1.8
Request of primary care physician or investigator	.	.	.	.	1	0.3	2	0.7	3	0.3
Protocol violation	.	.	.	.	1	0.3	1	0.3	2	0.2
Need for additional anti-PD treatment	10	3.4	2	0.7	2	0.7	2	0.7	16	1.4
Failed to return / lost to follow-up	1	0.3	1	0.3	.	.	1	0.3	3	0.3
Adverse events	7	2.3	9	3.1	10	3.4	11	3.8	37	3.2
Other	1	0.3	.	.	.	.	.	.	1	0.1
Termination of The PC phase*	270	90.6	273	94.8	275	93.2	273	93.2	1091	92.9

* This category includes subjects who entered into the active-treatment phase after completing the placebo phase and subjects who transferred early from the placebo phase.

Table B4. ADAGIO: Patient Premature Termination During Active-treatment Phase

ADAGIO	1 mg Delayed Start (N=298)		1 mg Early Start (N=288)		2 mg Delayed Start (N=295)		2 mg Early Start (N=293)		All	
	N	%	N	%	N	%	N	%	N	%
Entered into active-treatment phase	270	100.0	273	100.0	275	100.0	273	100.0	1091	100.0
Completed the study	231	85.6	238	87.2	241	87.6	244	89.4	954	87.4
Reasons for premature termination:										
Subject withdrew consent	8	3.0	3	1.1	1	0.4	2	0.7	14	1.3
Protocol violation	1	0.4	.	.	1	0.4	.	.	2	0.2
Need for additional anti-PD treatment	26	9.6	26	9.5	25	9.1	22	8.1	99	9.1
Failed to return/lost to follow-up	.	.	.	.	1	0.4	1	0.4	2	0.2
Adverse events	3	1.1	5	1.8	6	2.2	3	1.1	17	1.6
Death	.	.	1	0.4	.	.	.	.	1	0.1
Other	1	0.4	.	.	.	.	1	0.4	2	0.2

Table B5. TEMPO: Distribution of Patients by Use of Additional Dopaminergic Therapy during the Active-Treatment Phase

TEMPO	1 mg (N=124)		2 mg (N=124)		Placebo /2 mg (N=132)	
	N	%	N	%	N	%
ALL	40	32.3	45	36.3	40	30.3
AMANTADINE HYDROCHLORIDE	4	3.2	4	3.2	2	1.5
CARBIDOPA	11	8.9	14	11.3	17	12.9
CARBIDOPA MODIFIED-RELEASE	1	0.8	1	0.8	6	4.5
LEVODOPA	11	8.9	13	10.5	14	10.6
LEVODOPA MODIFIED-RELEASE	1	0.8	1	0.8	6	4.5
PERGOLIDE MESYLATE	2	1.6	2	1.6	2	1.5
PRAMIPEXOLE	17	13.7	22	17.7	20	15.2
ROPINIROLE HYDROCHLORIDE	7	5.6	5	4.0	4	3.0

Appendix C. Methodology for Natural History Staggered Start Analysis

A new analysis method is proposed that is referred to as the Natural History Staggered Start analysis (NHSS) with an estimator that is referred to as the Natural History Estimator (NHE) or Disease Modification (DM) estimate. Disease modifying and symptomatic effects can both cause slope differences between the treatment and placebo groups; therefore, information on how much the symptomatic effects of the treatment change over time (or with disease severity) could be used to reduce the bias is the group difference in slopes as an estimate of the disease modifying effect. Although there is no way to directly measure how much the symptomatic effects are changing over time, the NHSS approach uses the relationship between the baseline scores and the immediate (symptomatic) response to estimate these changing symptomatic effects. The NHE adjusts the estimated slope difference between the treatment and placebo groups to account for these changing symptomatic effects.

For instance, suppose the symptomatic (short-term) effect is larger for patients with more severe disease (higher UPDRS scores at baseline) with each additional point on the UPDRS score at baseline resulting in a symptomatic effect that is 1/4 point larger (τ_1=1/4). Then during the study, as the treated group is getting more severe, this same effect would separate the groups over time. If the delayed start group declined by 6 points during the placebo phase, then they would be expected to have an initial symptomatic effect that was 1.5 points (6*1/4=1.5) larger than the early start group by the time they go onto active treatment during the second phase.

The following assumptions are made when fitting the statistical model described below, using the NHSS method to estimate NHE, and interpreting the NHE in the context of disease modification:

1. All treatment effects that happen quickly are symptomatic effects and all treatment effects that accumulate over a longer time are disease-modifying effects. All symptomatic effects have been fully established prior to the first time point for which data are included in the model. If there are data collected prior to the time when symptomatic effects may have not been fully established, they will be excluded from the analysis.
2. A linear or quadratic model adequately fits the responses (changes from baseline) over time. If there are more than 3 measurements that are made after the symptomatic effect has been fully established, then a quadratic term should be considered (this leads to a slight modification of the NHE given below). If there are 3 measurements made in this time frame, then a linear model is

recommended since a quadratic model is not stable. If 2 or fewer measurements are made in this timeframe, then this model is not appropriate to fit.

3. There is a linear relationship between baseline clinical score and the symptomatic effect. If this relationship is assumed to be quadratic, then an adjustment to the NHE must be made to account for this.

4. The slope describing this cross-sectional relationship is the same as that describing the unidentifiable longitudinal relationship between evolving clinical score and the symptomatic effect over time.

5. In order for the NHE to be totally unbiased, one would have to also assumes that the clinical score is an accurate representation of the true disease state of the patient, without measurement error, but this assumption has only a minor effect on the results as long as the baseline population has a much larger variance than the measurement error.

6. It is also assumed that the symptomatic effect does not depend on other time-related factors such as age, chronological time, and increasing plasma concentration of drug over time. These assumptions can be tested with the clinical trial data.

Statistical Model and Derivation of the Natural History Staggered-Start Disease Modification Estimate

Let x be an indicator of treatment assignment (x=1 if the patient is assigned to treatment, x=0 if assigned to placebo) and let y_0 be the centered baseline value of the clinical outcome (difference between a patient's baseline value and the overall baseline mean). The model for the mean change from baseline in the clinical outcome at post-randomization time k, denoted t_k and measured in years for simplicity, can be written as a simple linear model:

$$\mu_k = \alpha_0 + \alpha_1 x + \tau_0 y_0 + \tau_1 x\, y_0 + \beta_0 t_k + \beta_1 x t_k + \gamma_0 y_0 t_k + \gamma_1\, x\, y_0 t_k,$$

and the model for the change from baseline for an individual can be written as:

$$\Delta\, y_{ik} = \alpha_0 + \alpha_1 x_i + \tau_0 y_{i0} + \tau_1 x_i\, y_{i0} + \beta_0 t_k + \beta_1 x_i t_k + \gamma_0 y_{i0} t_k + \gamma_1\, x_i\, y_{i0} t_k + e_{ik}$$

In the model above, $\alpha 1$ and $\tau 1$ correspond to symptomatic effects, and β_1 and $\gamma 1$ correspond to disease-modifying effects but also include effects due to the changing magnitude of symptomatic effects over time. The parameter β_0 is the slope of the placebo group and β_1 is the difference in the slopes of the treatment and placebo groups for a patient of average severity at baseline. The parameter γ_0 is the change in the slope of the placebo group associated with a one point increase in severity at baseline, and γ_1 is the change in the difference in slopes between the treatment and placebo groups associated with a one point increase in severity at baseline. Let φ be the difference in the slopes between the treatment group and the placebo group due solely to a disease-modifying effect, for a patient of average

severity at baseline, reported as points per year. The slope of the treatment group is $\beta_0 + \beta_1$ and the slope of the treatment group excluding symptomatic effects, i.e., the mean change in the "true" disease severity per year, is $\beta_0 + \varphi$.

We want to estimate φ by taking the difference in slopes between the treatment group and the placebo group (β_1) and subtracting the impact on the slope of the change in symptomatic effect over time. The NHE estimates the disease modification effect, φ, for an "average" patient in the study, so the parameter estimates of γ_0 and γ_1 are not incorporated in the NHE. The symptomatic effect over time is estimated by using the slope of the linear relationship between baseline score and the short-term symptomatic effect. This slope, $\tau 1$, is the average change in the magnitude of the symptomatic effect of treatment per one unit increase in baseline severity score. According to Assumption #3 above, this is also equal to the mean change in symptomatic effect that would occur in an individual patient due to a one unit increase in the "true" disease severity over time. Since the mean change in "true" disease severity per year in the treatment group is $\beta_0 + \varphi$, the mean change per year in symptomatic effects due to a change of $\beta_0 + \varphi$ units of "true" disease severity is equal to $(\beta_0 + \varphi) \times \tau_1$. So $\left(\hat{\beta}_0 + \text{NHE}\right) \times \hat{\tau}_1$ is an estimate of the amount that changing symptomatic effects are contributing to the slope difference between the active and placebo groups over time.

The NHE is calculated by taking the difference in slopes between the treatment and placebo groups and then subtracting the estimated symptomatic contribution to this slope difference:

$$NHE = \hat{\beta}_1 - \left(\hat{\beta}_0 + NHE\right) \times \hat{\tau}_1$$

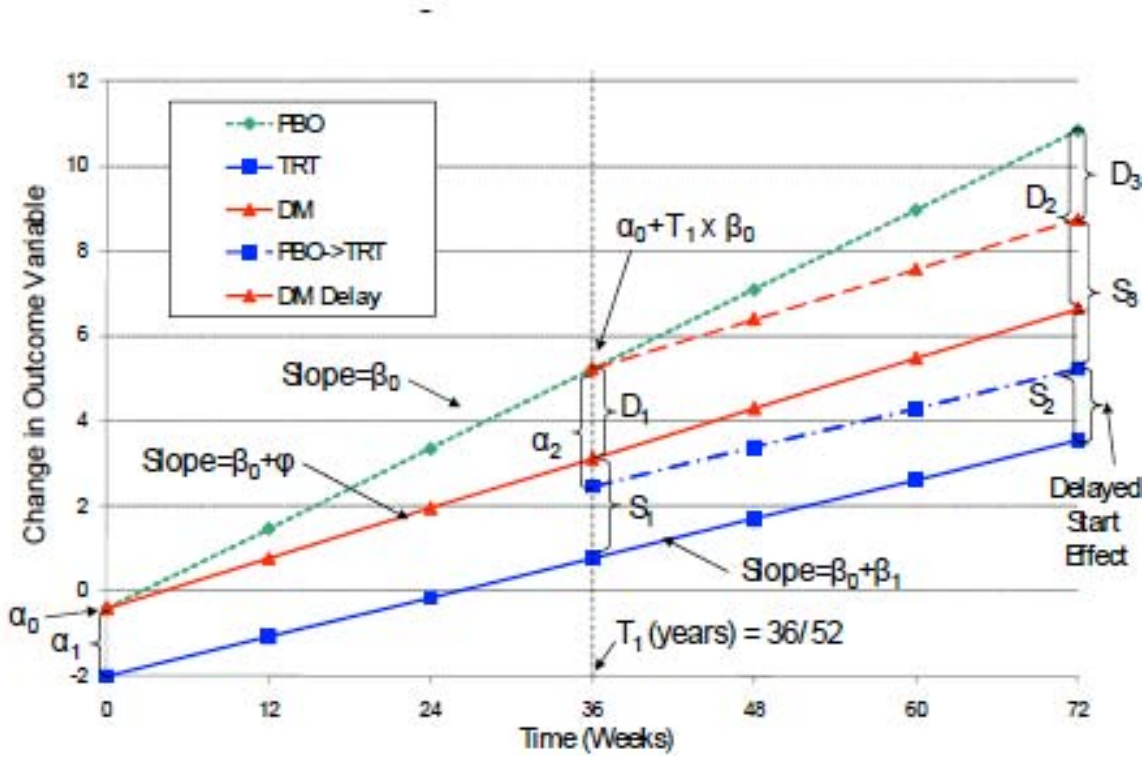
One then solves for NHE:

$$NHE = \frac{\hat{\beta}_1 - \hat{\beta}_0 \hat{\tau}_1}{1 + \hat{\tau}_1}$$

Since time is measured in years (for simplicity), the NHE can be interpreted as the number of points per year of treatment-related benefit (relative to placebo) due to disease modification, or specifically based on the proposed definition of disease modification, the treatment benefit that is accumulating over time. The standard error of this estimate can be estimated using a bootstrap procedure: resampling with replacement from the original data set and calculating the standard error (SE) of the distribution of the NHE from this resampling procedure. If τ_1 is zero, then the symptomatic effect does not depend on disease severity, and the NHE estimate is just the difference in slopes over 1 year. If τ_1 is negative, then as the disease gets worse, the symptomatic effect gets larger and the slope difference must be decreased in order to estimate the disease modifying effect. Ninety-five percent confidence intervals for the NHE are then obtained as NHE ± 1.96 × SE after verifying that the bootstrap distribution of the NHE is approximately normally distributed.

The slope of the DM effect is $\beta_0 + \varphi$, since φ represents a change in the slope (decline rate) from the placebo group (see Figure 17). The observed disease modification effect size can be represented as a percent reduction in decline, calculated as NHE / β_0.

Figure 17. NHSS Model Parameters



S_1 is the symptomatic effect for the Early-Treatment Group at the end of the first phase

D_1 is the disease-modifying effect for the Early Treatment Group at the end of the first phase

S_2 is the symptomatic effect for the Early-Treatment Group at the end of the second phase

D_2 is the disease-modifying effect for the Early-Treatment Group at the end of the second phase

S_3 is the symptomatic effect for the Delayed-Start Group at the end of the second phase

D_3 is the disease-modifying effect for the Delayed-Start Group at the end of the second phase

The Delayed-Start effect is estimated as $(D_2 + S_2) - (D_3 + S_3)$, and is intended to be an estimate of D_1. If the total incremental effect obtained during the second phase (the entire symptomatic effect and the disease-modifying effect acquired during the second phase) is the same for the early start group $[(D_2+S_2) - D_1]$ and the delayed-start group $(D_3 + S_3)$, then the

expected value of the Delayed Start estimate is equal to D_1 and the Delayed-Start estimate is an unbiased estimate of the disease-modifying effect at the end of the first phase. If this is not the case, then the Delayed-Start estimate is biased.

τ_1 is the difference in slopes that is due to symptomatic effects – it does not change over time or with differing baseline severity. α_2 is the initial symptomatic effect for the delayed start group and is bigger than α_1 which is the initial symptomatic effect for the early-start group. Although this figure does not illustrate the effect of γ_1, the slope for delayed-start patients may be worse or better than the slope of early-start patients when γ_1 is not equal to 0.

Analyses of the ADAGIO and TEMPO using the Natural History Staggered-Start Method

The Natural History Estimator is designed to be based on data collected from a single phase placebo-controlled study. The first phase of the ADAGIO study (0 to 36 weeks) and the first phase of the TEMPO study (0 to 26 weeks) are placebo controlled, and are therefore appropriate for this analysis (model 2). However, the ADAGIO and TEMPO studies also include a delayed start phase, and a modification to the approach would allow inclusion of data from this second phase of the study as well. An additional data set was analyzed that included second phase data for early start patients (model 1). Results from model 1 were considered primary because they include as much data as possible for patients who remained on the original randomized groups..

Additional analyses were performed using the second phase data from delayed start patients, however, these models were later found to have inflated Type 1 error rates in simulations and are not included.

For all analyses, the efficacy ITT population was used which included all subjects who had post-baseline efficacy data. Models were run separately for the 1 mg group versus placebo and the 2 mg group versus placebo. An unstructured covariance structure (UN) was specified for each model run. If the model was unable to converge using UN, then an ARH(1) structure or an AR(1) structure would be specified.

Model 1: “Placebo vs. Early Treatment” includes data from the first phase of the study plus continuing data from the second phase for patients who started treatment early (excludes second phase data for delayed start patients).

Model 2: “First Phase Only” includes only data from the placebo controlled phase of the study.

Both models were run on the 1 mg and 2 mg groups for ADAGIO, and TEMPO.

For each of the models above, a mixed model analysis, with actual time of the visit as a continuous covariate in the model, was run using PROC MIXED in SAS Version 9.2:

```
proc mixed data=UPDRS_Effic;

  class druggp pat hosp1 timeyrs;

  model cUPDRS = druggp hosp1 basecent druggp*basecent trtyrsq druggp*trtyrsq
druggp*trtyrsq*basecent / solution noint htype = 1;

  repeated timeyrs / subject = pat type = UN;

  lsmeans druggp / pdiff = all at (basecent trtyrsq)=(0,0);

run;
```

where

druggp = Treatment Group

pat = Patient

hosp1 = Site

timeyrs = Scheduled Time of Visit (years)

basecent = Centered Baseline UPDRS Score

cUPDRS = Change from Baseline in UPDRS Score

trtyrsq = Years on Current Treatment (quantitative) (Actual Time on treatment)

Scheduled time of the visit (categorical variable) was included in the REPEATED statement for modeling the covariance structure. Data collected within 12 weeks after initiation of study medication were excluded from the analyses, as were data from the TEMPO study that were collected after initiation of additional anti-PD treatment (patients who initiated additional anti-PD treatment in the ADAGIO study were to be discontinued at the time of initiation). The NHE was calculated based on parameter estimates from the fitted statistical model.

The standard error of the NHE was estimated using a bootstrapping procedure that re-sampled from the original data set with replacement. The bootstrap distribution of the NHE was assessed and found to be close to normal. Ninety-five percent confidence intervals were then calculated based on the estimated standard error, assuming normality. Observing whether 0 is contained in the confidence interval is equivalent to performing a two-sided test using a 5% significance level. No adjustments for multiple comparisons were made.

Simulations

In order to assess the type I error rate of the NHE and the bias, various scenarios were tested in a simulation study, including scenarios with no treatment effect, a symptomatic effect only, a disease modifying effect only and both symptomatic and disease modifying effects together. These scenarios were generated to correspond to the parameters seen in the ADAGIO study including similar correlation over time and similar dropout patterns. Analysis of these scenarios demonstrated that the NHSS methodology generally controlled the type 1 error rate and also had minimal bias in most cases.