A Randomized, Double-Blind, Placebo-Controlled, Delayed Start Study to Assess Rasagiline as a Disease Modifying Therapy in Parkinson's Disease (The ADAGIO Study): Rationale, Design, and Baseline Characteristics

C. Warren Olanow, MD,[1]* Robert A. Hauser, MD,[2] Joseph Jankovic, MD,[3] William Langston, MD,[4] Anthony Lang, MD,[5] Werner Poewe, MD,[6] Eduardo Tolosa, MD,[7] Fabrizio Stocchi, MD,[8] Eldad Melamed, MD,[9] Eli Eyal, PhD,[10] and Olivier Rascol, MD[11]

[1]*Department of Neurology, Mount Sinai School of Medicine, New York, New York, USA*

[2]*Parkinson's Disease and Movement Disorders Center, University of South Florida, Tampa, Florida, USA*

[3]*Department of Neurology, Baylor College of Medicine, Houston, Texas, USA*

[4]*The Parkinson's Institute, Sunnyvale, California, USA*

[5]*Department of Neurology, Toronto Western Hospital, Toronto, Ontario, Canada*

[6]*Department of Neurology, Innsbruck Medical University, Innsbruck, Austria*

[7]*Movement Disorder Unit, Neurology Service, Hospital Clinic, University of Barcelona, Spain*

[8]*Institute of Neurology, IRCCS San Raffaele Pisana, Rome, Italy*

[9]*Department of Neurology, Rabin Medical Center, Beilinson campus, Petah Tikva and Sackler, School of Medicine, Tel Aviv University, Israel*

[10]*Global Statistics Unit, Teva Pharmaceutical Industries Ltd, Israel*

[11]*INSERM U455, Clinical Investigation Center and Departments of Clinical Pharmacology and Neurosciences, Faculté de Médecine, Toulouse, France*

Abstract: A neuroprotective therapy is the single most important unmet medical need in Parkinson's disease. Several promising agents in the laboratory have been tested in the clinic, but none has been established in clinical trials to have a disease modifying effect despite positive results because of potential confounding symptomatic or pharmacologic effects. The delayed start design was developed to try to avoid a symptomatic confound when testing a putative neuroprotective therapy. In this study design, patients are randomly assigned to study drug or placebo in the first phase of the study, and both groups receive the active drug in the second phase. If benefits seen at the end of phase I persist through the end of phase II, they cannot be readily explained by a symptomatic effect (as patients in both groups are receiving the same medication) and benefits in the early start group must relate to the early initiation of the treatment. Although the precise mechanism responsible for such an effect can be debated, positive results in a delayed start study indicate that patients who receive early treatment have a better outcome than those where

the treatment is delayed. We are using the delayed start design to assess the potential disease modifying effects of rasagiline in a prospective double blind controlled trial (the ADAGIO study). We here describe the rationale for the study and baseline charac-

teristics of the 1,176 patients who have been enrolled into the trial. © 2008 Movement Disorder Society

Key words: Parkinson's disease; delayed start design; rasagiline; neuroprotection; disease modification

Parkinson's disease (PD) is the second commonest age-related neurodegenerative disorder, affecting 1 to 2% of persons over the age of 60 years. Current therapy is primarily based on a dopamine replacement strategy.[1,2] However, chronic levodopa treatment is associated with the development of potentially disabling motor complications in up to 90% of patients.[3] In addition potentially disabling features such as gait dysfunction, loss of balance, freezing, sleep disturbances, autonomic disorders, and dementia are often not satisfactorily controlled with available therapies.[1,4] These levodopa nonresponsive features are thought to reflect nondopaminergic pathology in the brain, spinal cord, and peripheral autonomic nervous system.[5,6] Indeed, prospective long-term studies indicate that levodopa nonresponsive features are the primary source of disability and nursing home placement in advanced patients.[7] Thus, many PD patients suffer disability despite currently available therapies. The development of a neuroprotective therapy that slows, stops, or reverses disease progression is the highest priority in PD research.

Numerous agents have been considered to have putative neuroprotective effects based on laboratory research, but none has been established to provide a neuroprotective effect in PD despite clinical trials with positive outcome measures.[8] One of the major limitations in defining a neuroprotective therapy has been the lack of an outcome measure that accurately reflects the underlying disease state and is not confounded by symptomatic or pharmacologic effects of the study intervention. The MAO-B inhibitor rasagiline (Azilect®) has been demonstrated to be an anti-apoptotic agent that has neuroprotective effects in laboratory models.[9] Further, results of the TEMPO clinical trial were consistent with the possibility that rasagiline might have a disease modifying effect in PD.[10,11] However, rasagiline has been demonstrated to provide statistically significant antiparkinsonian benefits when used as monotherapy in early PD[10] or as an adjunct to levodopa in PD patients experiencing motor fluctuations,[12,13] and thus might be expected to introduce a symptomatic confound into a neuroprotective study using outcome measures that have been employed to date. To further explore the possibility that rasagiline has a disease

modifying effect in PD, and to try and avoid confounding symptomatic effects, we have organized the ADAGIO study, a prospective, multicenter, placebo-controlled, double-blind clinical trial utilizing the delayed start design. This article will describe the rationale, study design, and baseline characteristics of patients participating in the ADAGIO study.

RASAGILINE

Rasagiline [*N*-propargyl-(1*R*)-aminoindan] is a secondary cyclic benzylamine and indane derivative which provides irreversible, potent MAO-B inhibition.[14] Rasagiline incorporates a propargyl ring within its molecular structure suggesting that it could have neuroprotective effects. Preclinical studies have demonstrated that propargylamines can protect neurons from a variety of toxins in both in vitro and in vivo models.[9,15] Rasagiline has been shown to protect neurons in vitro from the nitric oxide donor 3-morpholinosydnonimine hydrochloride (SIN-1), glutamate, 6-hydroxydopamine, growth factor deprivation, and *N*-methyl-(*R*)salsolinol.[16–21] Rasagiline also protects dopamine neurons in rodents from 6-OHDA[22] and in primates from MPTP toxicity.[23] Rasagiline promotes the recovery of motor function and spatial memory and reduces cerebral edema after closed head injury in the mouse,[24] improves neurologic severity and the volume of necrotic brain tissue after middle cerebral artery occlusion in the rat,[25] and increases survival of the G93A Cu/Zn SOD transgenic mouse model of ALS.[26]

Protection associated with rasagiline is thought to be related to an anti-apoptotic effect associated with its propargyl ring rather than MAO-B inhibition.[27,28] Indeed, protective effects have been obtained with its (*S*)-enantiomer which lacks MAO-B inhibitory activity.[24,29,30] Substantial evidence indicates that propargylamines exert their anti-apoptotic effects by way of an interaction with glyceraldehyde-3-phosphate dehydrogenase (GAPDH),[27,31] an intermediary enzyme in glycolytic metabolism that is also involved in protein translation. Mitochondrial stress leads to the displacement of GAPDH from its binding site on stem loop RNAs and increases cytoplasmic levels of GAPDH. GAPDH normally exists as a tetramer, in which form

it translocates to the nucleus and blocks transcriptional upregulation of anti-apoptotic molecules such as SOD-1, SOD-2, Bcl2, and BclXL.[31,32] Rasagaline binds to GAPDH and maintains it as a dimer, in which form it does not translocate to the nucleus, thereby permitting cells to upregulate protective molecules such as BCL-2 which prevent oxidative stress, maintain the mitochondrial membrane potential, and block apoptosis.[21,33–37]

NEUROPROTECTIVE TRIALS IN PD

Clinical trials have examined several promising compounds to determine if they have disease modifying effects in PD.[8] Several were negative showing no effect of the study drug on the outcome measure; however some were positive but could not be established to be neuroprotective because of the potential that the outcome measure was confounded by a symptomatic or pharmacologic effect of the study intervention. In the DATATOP study the primary endpoint was the time to development of disability necessitating levodopa therapy.[38] However it could not be determined if positive results in this trial were due to selegiline having a protective effect that slowed degeneration or a symptomatic effect that masked it.[39] The primary endpoint in the SINDEPAR study was the change in UPDRS motor score between untreated baseline and an untreated final visit performed after 12 months of treatment with selegiline or placebo and 2 months of drug wash-out.[40] Patients treated with selegiline had less deterioration from baseline than patients treated with placebo, but a confounding long-duration symptomatic effect lasting longer than 2 months could not be excluded. More recently, TCH346, a novel propargylamine was studied as a possible neuroprotective agent. In the laboratory, TCH346 was observed to have protective effects in both *in vitro and in vivo* models, even when administered in low doses.[41–43] As TCH346 did not induce MAO-B inhibition, there was optimism that the drug would not be confounded by symptomatic effects. The drug was tested in a prospective, double-blind, placebo-controlled multicenter trial using time to need for levodopa as the primary endpoint.[44] At the three doses tested, TCH346 did not demonstrate a positive effect on any of the primary or secondary endpoints. These results do not support a disease modifying role for this compound and raise the question as to whether benefits obtained with other propargylamines might be symptomatic rather than protective. On the other hand, it is noteworthy that patient randomized to receive selegiline versus placebo had better long term UPDRS scores and less freezing.[45]
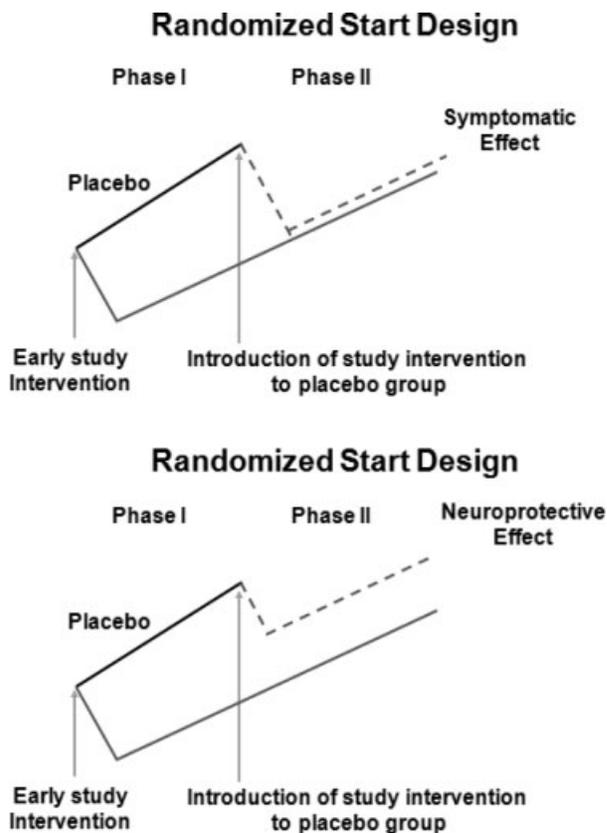

FIG. 1. The delayed start design. Schematic representation of some possible outcomes of the delayed start study. In both panels, the study intervention is shown to provide a benefit in comparison to placebo at the end of phase I, but it cannot be determined if this benefit is due to a symptomatic or protective effect, or a combination of the two. The top panel illustrates that introduction of study drug to the original placebo group provides a benefit that allows the group to "catch up" and is comparable to that seen in the early start group. In this model, benefits could be entirely related to a symptomatic effect. The bottom panel illustrates the case where introduction of study intervention to patients in the placebo group (delayed start) does not provide benefit equal to that observed in subjects in the early start group and this difference persists over several study visits. Thus, the delayed start group does not catch up to the early start group and the slopes of the rate of progression does not converge (i.e. lines remain parallel). This result cannot be readily explained by a symptomatic benefit and is consistent with the study intervention having a neuroprotective or disease modifying effect.

To avoid the confounding symptomatic effects of the dopamine agonists ropinirole or pramipexole, the REAL-PET and CALM-PD-CIT studies used rate of decline in a neuroimaging surrogate biomarker of nigrostratial function as the primary endpoint.[46,47] Both studies showed that treatment with the dopamine agonist was associated with a significant reduction in the rate of decline of the imaging biomarker in comparison to levodopa. As there was no placebo group, the study could not differentiate between a protective effect provided by the agonist or toxicity caused by levodopa.

However, the possibility that study results could have been due to differences in the pharmacologic effect of these drugs on the biomarker rather than on cell survival or function could not be excluded.[48]

To address the problems with existing trial designs aimed at detecting neuroprotection, the delayed start design has been proposed[49] (Fig. 1). Here, patients are randomized to initiate treatment with study drug (early start) or placebo for a fixed time interval (phase I). Thereafter, patients in the placebo group are initiated on the active study drug (delayed start), so that patients in both study groups are on the same treatment, and patients are followed for another fixed time interval (phase II). Differences between the two groups at the end of phase I could be due to symptomatic and/or neuroprotective effects. If, however, an initial difference between the two groups at the end of phase I is sustained at the end of phase II when patients in both groups are receiving the same study drug, this would mean that early treatment conferred a benefit that could not be equaled with later introduction of the same drug.

A delayed start component was added-on to the TEMPO study,[10] which was primarily designed as a 6 month study in early untreated PD patients to assess the safety and efficacy of rasagiline in comparison to placebo. At the end of 6 months, patients in both groups were treated with rasagiline and followed for an additional 6 months. Benefits observed at the end of the first 6 months in the early rasagiline treatment group persisted at the end of 12 months. This difference cannot be readily explained by a symptomatic effect because patients in both groups were on the same treatment at the final visit.

THE ADAGIO STUDY

The ADAGIO study is the first prospectively designed clinical trial to test the potential of rasagiline to have a disease modifying effect in a delayed start study. ADAGIO is a multicenter, double-blind, placebo-controlled, study involving patients with early untreated idiopathic PD.

Patients

Untreated PD patients of either sex and any race could be included in this study. Diagnosis was based on having two cardinal signs (resting tremor, bradykinesia, rigidity), and if rest tremor was not present subjects must have unilateral onset with persistent asymmetry. Patients with atypical or secondary parkinsonism were excluded. Other entry criteria included
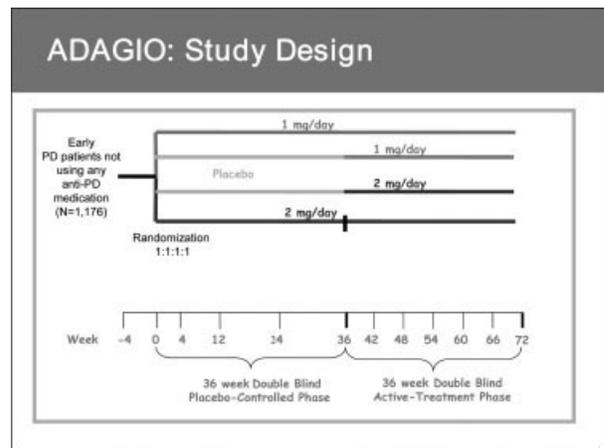
FIG. 2. Schematic representation of study outline and visits.

disease duration of less than 18 months from time of diagnosis and a determination in the best judgment of the investigator that the patient would not require treatment in the subsequent 9 months. Patients with >3 weeks of treatment with any anti-parkinsonian medication prior to baseline were not eligible for the study. Prior use of rasagiline, selegiline, or coenzyme Q10 (in daily doses >300 mg) within the previous 120 days was prohibited.

Study Design

The ADAGIO study is comprised of two phases: phase I, 36-week double-blind, placebo-controlled; and phase II, 36-week double-blind, active-treatment phase in which all patients are on active study intervention. After obtaining IRB-approved informed consent, subjects were randomized in a 1:1:1:1 ratio into one of the following four treatment groups, based on a computer generated randomization scheme with blocks stratified by center (see Fig. 2):

1. 1 mg/day rasagiline during phase I and phase II (1 mg early start)
2. 2 mg/day rasagiline during phase I and phase II (2 mg early start)
3. Placebo during phase I followed by 1 mg/day rasagiline during phase II (1 mg delayed start)
4. Placebo during phase I followed by 2 mg/day rasagiline during phase II (2 mg delayed start)

Thus, "early-start" patients receive 72 weeks of treatment with rasagiline (1 or 2 mg once daily) and

"delayed-start" patients receive 36 weeks of placebo followed by 36 weeks of rasagiline (1 or 2 mg once daily). The 36-week duration of phase I, the placebo-controlled period, was estimated to be long enough to establish a difference between active treatment and placebo, and a time period during which the average patient could remain on placebo without needing symptomatic therapy. If subjects in either treatment group required additional anti-parkinsonian medication during the placebo-controlled phase of the trial, they could proceed directly to Phase II. Once in Phase II, no additional anti-PD therapy is permitted. If the patient requires additional medication in this stage they are discontinued from the study.

Visits and Evaluations

Visits are performed at time points indicated in Figure 2. At each visit except at week 4, a UPDRS evaluation is performed. Prior to enrolling study subjects, each rater was required to successfully pass a certification program for the motor section of the UPDRS based on the Movement Disorder Society Teaching Tape. At the end of the teaching section, raters evaluated four PD patients and scored all items (except rigidity). To pass the exercise, the raters had to provide total UPDRS motor scores that fit within the 95% CI of the scores provided by three experts. Ninety-six percent of candidates passed on their first or second attempts.

Other evaluations performed at each visit included measures of quality of life, adverse events reporting, and standard laboratory assessments.

Safety and Tolerability

Tolerability is assessed by the number of subjects (%) who discontinue the study and the number of subjects who discontinue the study because of adverse events (AEs). Safety assessments include incidence of adverse events, laboratory values, vital signs, home blood pressure monitoring, ECG, physical and neurological examination, and skin examination by a qualified dermatologist.

Endpoints, Statistical Analysis, and Sample Size

The analysis plan for the ADAGIO study will be finalized with the FDA prior to locking the data base. The principal statistical analysis will incorporate three primary efficacy hypotheses tests which will analyze in a hierarchical manner the change from baseline in total UPDRS score (sum of parts I, II, and III). Hierarchal endpoints involve testing multiple hypotheses in a sequential manner. The first primary efficacy hypothesis will compare the rate (slope estimate) of UPDRS progression during the placebo controlled phase from week 12 to week 36 between the placebo- and rasagiline-treated arms (1 and 2 mg groups). The second primary efficacy hypothesis will compare the estimate of change from baseline to week 72 in total UPDRS score between the rasagiline early start and delayed start groups for each dose (1 and 2 mg). The third hypothesis will test for noninferiority of the slope estimates of the early-start and delayed-start rasagiline groups (1 and 2 mg) during the active phase of the trial (weeks 48–72). This analysis will determine if any separation between the groups at the end of phase I persists, or if the slopes of the curves tend to converge. For the study to be declared positive, the early treatment group must demonstrate in comparison to the delayed start group a) superiority of slopes from week 12 to 26, b) superiority of change between baseline and week 72, and c) non-inferiority of slopes between weeks 48 and 72. The secondary endpoint is the change in total UPDRS scores between baseline and final visit of Phase I. Additional endpoints include the number (%) of subjects who need additional anti-parkinsonian therapy, and the time until additional anti-parkinsonian therapy is required. The 1 and 2 mg rasagiline dose groups will be analyzed separately and will not be pooled. On the basis of the results of the TEMPO study[10,11] a total of 1,100 subjects will provide more than 85% power to meet all three primary analyses.

Mixed models repeated measures analysis of covariance will be used for all hypothesis statistical tests and parameter estimates. The model will include the following fixed effects: treatment group, week in trial, week by treatment interaction, center, and baseline total UPDRS score. To maintain an experiment-wide type I error of 0.05, the Hochberg-Step up Bonferoni method will be used to account for multiple comparisons between treatment groups and the hierarchal method will be used to account for multiple primary analyses.[50]

For the first primary analysis, all patients will be included in an intention to treat (ITT) population. For the second and third analyses we will include all subjects entering the active treatment phase with at least 24 weeks of treatment during the placebo controlled phase and at least one available UPDRS measurement during the active treatment phase from week 48 onwards. All safety analyses will be reported using the ITT population.

BASELINE RESULTS

The study was initiated in November 2005 and enrolment was completed in December 2006. A total

TABLE 1. *Baseline demographics (1,176 patients)*

	Mean	SD	Min	Median	Max
Age (years), all	62.2	9.6	31.2	63.0	80.9
Time from PD diagnosis (months)	4.5	4.6	0.0	2.7	18.0
UPDRS total (range: 0–176)	20.4	8.5	3.0	19.0	53.0
UPDRS Part I (range: 0–16)	1.0	1.2	0.0	1.0	8.0
UPDRS Part II (range: 0–52)	5.2	3.0	0.0	5.0	17.0
UPDRS Part III (range: 0–108)	14.2	6.4	2.0	13.5	39.5
Modified Hoehn and Yahr	1.5	0.5	1.0	1.5	2.5

of 1,176 patients from 129 active sites in 14 countries (Argentina, Austria Canada, France, Germany, Hungary, Israel, Italy, Netherlands, Portugal, Romania, Spain, UK, and USA) signed IRB-approved informed consent and were randomized to a treatment group. Baseline demographics are provided in Table 1. The mean age of subjects was 62.2 ± 9.6 years, there were 718 males (61.1%) and 458 women (38.9%), mean time from diagnosis was 4.5 ± 4.6 months, and the mean total UPDRS score was 20.4 ± 8.5. There were 83 terminations during the placebo phase (7%) so we anticipate having sufficient power to perform the final analyses.

DISCUSSION

Rasagiline is currently approved for the symptomatic treatment of PD. The molecular structure of the drug and laboratory studies suggests that the drug may also have neuroprotective or disease modifying effects. Indeed, a preliminary clinical trial suggested that it might also have disease modifying effects.[11] However, outcome measures that have been employed in clinical trials of putative neuroprotective effects to date have been confounded by potential symptomatic or pharmacologic effects of the study intervention. The delayed start design was developed in an attempt to avoid the problems of confounding symptomatic effects. The ADAGIO study is a prospective double-blind, placebo-controlled trial that employs a delayed start design. Neuroimaging was not used as an end-point in this study as it is likely that imaging markers are susceptible to confounding effects, and a better understanding of these markers is needed before clinically meaningful interpretation is possible.[51] Patient enrolment has been completed ahead of schedule and it is anticipated that final results will be available by the fourth quarter of 2008.

Positive results in the ADAGIO study will determine that early treatment with rasagiline provides benefits that cannot be attained with later initiation of the drug, and are sustained for at least 18 months. Whether these benefits will endure beyond that time remains to be determined, but it is noteworthy that benefits of early

rasagiline treatment seen in the TEMPO study persisted for up to 6.5 years, although follow up was open label and did not include all patients.[52] The mechanism responsible for such a benefit can be debated. Positive results in a delayed start study are consistent with the possibility that the treatment intervention has a neuroprotective effect and has slowed disease progression. It is theoretically possible that rasagiline has a slowly accumulating symptomatic effect, although one would assume that 9 months of active drug treatment in patients originally assigned to the placebo group should be sufficient to account for this eventuality. An alternate explanation for a positive result in the early treatment group is that early symptomatic treatment helps to maintain basal ganglia compensatory mechanisms associated with dopamine depletion and prevents decompensation that might otherwise occur and could not be made up for by later introduction of the drug.[53] Alternatively, early treatment could also prevent the development of maladaptive compensatory responses. These concepts could account for why early treatment with levodopa provided benefits that could not be equaled in patients who received early treatment with dopamine agonists even though they could receive supplemental levodopa at a later time if it was deemed necessary.[54,55] Similarly, this concept might account for the results observed in the ELLDOPA study where patients treated with levodopa for 9 months had superior benefits in comparison to placebo treated patients even after 2 weeks of drug washout.[56] Indeed, it has been suggested that efforts to normalize basal ganglia function and support endogenous compensatory mechanisms through early initiation of therapy might benefit patients through both symptomatic improvement and delaying clinical progression.[53] Regardless of the responsible mechanism, positive results in a delayed start study would indicate that early treatment provides benefits that cannot be equaled with later introduction of the same drug. Such results could have important implications for the management of PD.

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