ADAGIO (The Attenuation of Disease Progression with Azilect Given Once-daily). A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease

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Background: Therapy that slows the progression of PD is an unmet need. There has been some evidence, both in basic science and clinically, that MAO inhibitors may have a disease modifying effect. This clinical trial sought to show this clinical endpoint while also removing confounding effects of this drug as a symptomatic treatment. See attached document for a further detailed background.

Study Design (sponsored by the drug manufacturer, Teva Pharmaceuticals): Double, blind Randomly Controlled Delayed Start Trial. The decision to use a delayed start trial was made to remove the confounder of a medication that exerts symptomatic benefit to the disease (See DATATOP in Historical Background). There are two phases, phases 1 and 2. In phase 1, subjects are randomly assigned to placebo or treatment and differences in the group may be due to symptomatic effect of medication, disease-modifying effects or both. Persistent differences between the two groups after phase 2 would remove the confounder of symptomatic treatment, since both groups receive the same treatment, and would thus be due to disease modifying effect.

Site of study: Multi-center in 129 different centers across 14 countries.

Inclusion criteria: Diagnosis of PD based on 2 of 3 cardinal symptoms (resting tremor, bradykinesia, rigidity), age of 30-80yrs, and not currently receiving treatment for PD.

Exclusion criteria:

- **i.** Exposure to any anti-parkinsonian medication for more than 3 weeks
- **ii.** Prior use of MAO-inhibitor or CoQ within the previous 120 days
- **iii.** Disease duration >18 months
- **iv.** Hoehn and Yahr of stage 3 or higher

Intervention: 18-month study consisting of two phases, each of which were 36 weeks. In Phase 1, subjects were assigned to rasagiline 1mg, rasagaline 2mg, or placebo. In Phase 2, patients who received rasagiline would continue, while patients who received placebo were switched to rasagiline.

Assessment days: Visits performed at baseline and at weeks 4, 12, 24, 36, 42, 48, 54, 60, 66, and 72. At each visit, subjects were evaluated via the UPDRS; adverse events and vitals were also assessed.

Primary outcome: For each dose all three of the following endpoints had to be met to declare that the drug had disease modifying effect

- Change in slope of UPDRS between rasagiline groups (1mg and 2mg) and placebo from week 12-36
- Compared the estimated change in total UPDRS between baseline and week 72 in early start and delayed start (i.e., if the benefit seen in the early group was still present while both received same treatment)
- Non-inferiority of slope estimates for the rate of change from baseline in UPDRS between weeks 48 and 72 in early start as compared to delayed start

Results: Among subjects who received rasagiline at 1mg per day:

- The estimates of change in slope of UPDRS scores between weeks 12 and 36 showed a slower rate of worsening (0.09 +- .02 in treatment vs 0.14 +- .1 for placebo). ✓
- The early start group had less worsening in mean total UPDRS score between baseline and week 72 in early start (2.87 +- .53) than delayed start(4.50 +- .56). ✓
- The estimates of the change in UPDRS scores between 48 and 72 weeks showed noninferiority of the response in the early treatment group (.085 +- .02). ✓

Among subjects who received rasagiline at a dose of 2mg per day:

a. The estimates of change in slope of UPDRS scores between weeks 12 and 36 showed slower rate of worsening (0.07 +- .02 in treatment vs 0.14 +- .1 for placebo). ✓
b. The change in total UPDRS scores between baseline and week 72 in the early start (3.47 +- .5) did not differ significantly from delayed start (3.11 +- .5). ✗
c. The estimates of the rate of change in the UPDRS scores between weeks 48 and 72 showed noninferioirity of the response in the early start (.094 +- .01) as compared to delayed start (.065 +- .02) ✓

Conclusions: In order to qualify as having a disease modifying effect, significant benefits must be achieved in each of the three primary endpoints. This was met in the 1mg rasagiline group, but not the 2mg rasagiline group. Both groups had beneficial effects on symptoms as compared to placebo.

Theories on why disease-modifying effects were not met in 2mg:

a. In the laboratory, the protective effects of proparglyamines are characterized by a U-shaped curve and have a maximal concentration effect. However, the dwindling of the protective effects are seen in a logarithmic manner and are not expected between doses of 1mg and 2mg.
b. The symptomatic benefit of 2mg may have masked the benefit associated with early treatment in the population with very mild disease. In post-hoc analysis, patients in the highest quartile of UPDRS met all three criteria receiving 2mg of rasagiline.

The study showed a possible benefit of the early use of rasagiline at a dose of 1mg per day in preventing disease. However, given the negative findings in the 2mg dose, it could not be definitively concluded that rasagiline has disease-modifying effects. The authors suggested further studies in patients with more advanced disease to possibly remove this confounder. Still ADAGIO is considered a pinnacle study in PD, and many clinicians use this study to justify early treatment with Azilect, given its early symptomatic benefit and possible disease modifying effect at 1mg.

Summary created by Jon Isaacson, M.D.

Historical Background, ADAGIO

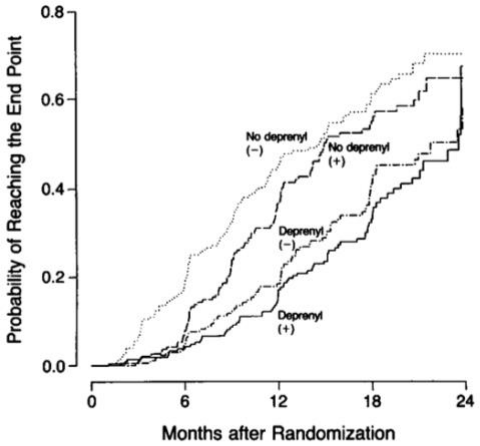
The 1960s saw the discovery of L-DOPA as a foundational weapon for the previous incurable and untreatable malady that was Parkinson's Disease. Initially framed a miracle cure, Levodopa worked as a trojan horse that was able to bypass the blood brain-barrier and allow dopamine to reach the brain and alleviate symptoms of PD. At the time whopping doses of L dopa were used in order to penetrate into the CNS, given its low penetration and peripheral uptake.

At the same time there was a new medication for the treatment of tuberculosis in 1950s called iproniazid, an irreversible MAOI. Not only were patients improving from tuberculosis on iproniazid, but they seemed to be inappropriately happy with enhanced mood and energy. This led to further studies evaluating its use in depression, and it became the first specific antidepressant. Eventually, it was theorized that it could be of potential benefit in PD if paired with L-DOPA, by delaying the breakdown of dopamine. Unfortunately, initial studies showed no benefit, and were plagued with the tyramine side effects when paired with cheese and wine including elevated BP, headache, and brain hemorrhages. This later led to the discovery of different forms of MAO, and specifically MAO-B as a specific inhibitor of the breakdown of dopamine. Later Jozsef Knoll, a Hungarian pharmacologist and physician, discovered L-Deprenyl, or Selegiline, as a specific MAO-B for the treatment of depression and mood, with markedly reduced "tyramine effect."

Moussa Youdim, an Iranian neuroscientist, showed the presence of high concentrations of MAO-B in the basal ganglia, and hypothesized that selegiline could be a valuable treatment in PD when paired with L-DOPA. Early studies showed just this as a beneficial effect was seen in the symptomology of PD, and thus a new treatment for PD was born.

Later in the 1980s, there was a young patient that arrived in the ED in California. The patient presented with acute onset of masked facies, cogwheel rigidity and minimal spontaneous activity. At first, he was presumed to have catatonic schizophrenia, but given an acute and odd presentation, neurology was consulted in the ED. The neurology resident, startled and perplexed, called the attending physician on call, Dr. Langston. Dr. William Langston, a Stanford neurologist, was befuddled at what could be causing these patients to be awake and alert but seemingly unresponsive. From the neurologist's perspective the forty-year-old patient appeared as though he had acutely developed features of advanced PD. Further investigations led to the same presentation in multiple other young patients in the area. At first, there was no obvious connection in terms of location or relationship, but later it was discovered that all patients were using a new form of synthetic heroin. They all seemed to respond to L-Dopa but had unpredictable responses and early motor fluctuations. The heroin was tested in the lab and found to all comprise a metabolite called MPTP. Dr. Langston et al published their findings in Science in 1983 hypothesizing that MPTP caused permanent parkinsonism in these patients, by exerting a toxic effect on the pars compacta of the substantia nigra. Further studies showed that the active metabolite of MPTP (called MPP+) destroys melanin-containing nerve cells in the midbrain and causes the syndrome of parkinsonism in non-human primates. Additional work led to the discovery that MPTP was taken up into the brain, mistaken by MAO for dopamine, and broken down to MPP+, which then exerts it's toxic effect. Jan Chiba used this to show that Selegiline does indeed block the conversion of MPTP to MPP+. Dr. William Langston then used Selegiline to pre-treat non-human primates before exposing them to MPTP and showed that they were protected from developing PD. These basic science discoveries led to the hypothesis that Deprenyl might prevent the accumulation of toxic free radicals in the substantia nigra which was hypothesized to cause the disease. This led to a subsequent DATATOP Trial to evaluate if Deprenyl can slow the progression of PD.

DATATOP was conducted in 1993 by The Parkinson Study Group, and sought to evaluate the effects of Tocopherol and on Deprenyl on the progression of early PD. As above, it was thought that the pathogenesis of PD might be secondary to the formation of free radicals causing degeneration of the substantia nigra. Thus, this study aimed to determine whether these interventions could extend the length of time before advancing disability in PD. In the study, 800 patients were split into four arms: a placebo, active tocopherol and placebo Deprenyl, active deprenyl and placebo tocopherol and active tocopherol and active Deprenyl. The primary end point was the onset of disability prompting the decision to start levodopa. The results of the trial showed no beneficial effect of tocopherol but saw beneficial effects of deprenyl which occurred in the first 12 months of treatment and delayed onset of levodopa treatment. The difference in the estimated median time to the end point was 9 months. It was thus concluded that Deprenyl at 10mg a day delayed the onset of disability associated with early untreated PD.



No deprenyl (−)	201	154	98	48	1
No deprenyl (+)	192	173	112	50	2
Deprenyl (−)	178	163	129	70	7
Deprenyl (+)	215	202	167	83	4

Figure 2. Kaplan–Meier Estimate of the Cumulative Probability of Reaching the End Point, According to Treatment with Deprenyl or without Deprenyl and to the Presence (+) or Absence (−) of Improvement in the One-Month Total UPDRS Score.

The period of analysis was the time from base line to the last evaluation during treatment. The number of subjects evaluated in each group is shown under each time point. See the Results section for hazard ratios and P values.

The study was deemed a success and lauded as possibly the first agent that could delay disability and have neuroprotective activity. Dr. Langston was quoted as saying, “For the first time, there is hope for patients with Parkinson’s disease.” Unfortunately, hope was soon curtailed when a long term analysis of results of the trial showed that disability scores diminished in the deprenyl-treated patients. Further, Dr. William Landeau wrote a scathing critique in his popular Clinical Neuro-mythology section of the Neurology Journal. He critiqued the premise that Deprenyl had a neuroprotective effect: this would only be the case if the molecule specifically effected disease progression and not only the symptoms itself. Prior studies had shown a symptomatic effect of Deprynl for the treatment of early PD (i.e., TEMPO trial). Thus, the trial would have required a delayed-start design as in other similar trials, to evaluate the progression of disease (e.g., studies that evaluate anticholinesterases in AD would use this approach since this drug class has symptomatic benefit to the disease). This led to the Adagio study being conducted in that manner.