Rasagiline for Slowing Clinical Progression in Parkinson’s Disease

Teva Pharmaceuticals
PCNSDAC
October 17, 2011
Rasagiline for Slowing Clinical Progression in Parkinson’s Disease

Dennis Ahern
CNS Therapeutic Area Regulatory Lead
Teva Branded Pharmaceutical Products
Azilect® (rasagiline)

- Approved in the U.S. since 2006
- Indicated for symptomatic treatment
- Available in 41 countries worldwide
- Has well-documented safety profile
  - >500,000 patient years of exposure
Teva Seeks an Expanded Indication for Rasagiline

- **Current Indication**
  - Azilect is indicated for the treatment of patients with idiopathic Parkinson’s disease (PD) to treat the signs and symptoms of PD as initial monotherapy and as adjunct therapy to Levodopa.

- **Proposed addition under sNDA**
  - Azilect is indicated for the treatment of patients with idiopathic Parkinson’s disease to slow clinical progression and treat the signs and symptoms of Parkinson’s disease as initial monotherapy and as adjunct therapy to levodopa.
Unmet Medical Need for Disease Modification Therapy

- Parkinson’s disease is a major public health problem
- Current therapies treat symptoms only
- There are no approved treatments for slowing or modifying disease progress
- Delayed-start trial design developed to separate symptomatic and disease-modifying effects
Two Randomized Delayed-start Trials Support Slowing Clinical Progression with Rasagiline

- ADAGIO supports rasagiline efficacy
  - 1mg dose demonstrates slowing of clinical progression
- TEMPO supports rasagiline efficacy
  - 1 and 2mg doses demonstrate slowing of clinical progression
- Data support favorable safety profile
- Data should be communicated to physicians and patients
# Agenda

## Medical Need

**C. Warren Olanow, M.D.**  
Henry P. and Georgette Goldschmidt Professor and Chairman Emeritus, Department of Neurology  
Professor, Department of Neuroscience  
Director, Robert and John M. Bendheim Parkinson’s Disease Center  
Mount Sinai School of Medicine, New York City

## TEMPO & ADAGIO Trials

**Cheryl Fitzer-Attas, Ph.D.**  
Director of Scientific and Medical Affairs  
Global Innovative Products  
Teva Pharmaceutical Industries, Ltd.  
Petah Tikva, Israel

## Interpreting the Rasagiline Delayed-start Studies

**C. Warren Olanow, M.D.**

## Q&A Moderator

**Cheryl Fitzer-Attas, Ph.D.**
# Additional Experts

## Teva

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Patrick Darken, Ph.D.</strong></td>
<td><strong>Ruth Levy, Ph.D.</strong></td>
</tr>
<tr>
<td>Head of Biostatistics</td>
<td>VP &amp; Head of Global Innovative Search and Evaluation</td>
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## External Consultants

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<tr>
<td><strong>Paul Feigin, Ph.D.</strong></td>
<td><strong>Werner Poewe, M.D.</strong></td>
</tr>
<tr>
<td>Professor – Statistics</td>
<td>Chairman, Department of Neurology</td>
</tr>
<tr>
<td>Technion - Israel Institute of Technology</td>
<td>University of Innsbruck, Austria</td>
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<tr>
<td>Haifa, Israel</td>
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<tr>
<td><strong>Mike McDermott, Ph.D.</strong></td>
<td><strong>Suzanne Hendrix, Ph.D.</strong></td>
</tr>
<tr>
<td>Professor - Department of Biostatistics and Computational Biology</td>
<td>Independent Biostatistician</td>
</tr>
<tr>
<td>University of Rochester School of Medicine and Dentistry, NY</td>
<td>President, Pentara Corporation, UT</td>
</tr>
</tbody>
</table>
Slowing Clinical Progression in Parkinson’s Disease

C. Warren Olanow, M.D.
Henry P. and Georgette Goldschmidt Professor and Chairman Emeritus, Department of Neurology Professor, Department of Neuroscience Director, Robert and John M. Bendheim Parkinson’s Disease Center Mount Sinai School of Medicine
Conflicts of Interest

- Ceregene
- Merck Serono
- Lundbeck
- Novartis
- Orion
- GSK
- Teva

- Clintrex
  - Abbott
  - CHDI
  - Civitas
  - Novartis
  - Phytopharm
  - Siena
  - Synagile
  - Synosia (Biotie)
  - Vectura
Parkinson’s Disease is a Major Public Health Problem

- Age-related neurodegenerative disorder (age of onset at ~60 years)
- Affects ~500,000 - 750,000 persons in United States
- Affects men and women of all races and all occupations
- Frequency expected to dramatically increase in the next several decades based on aging of the population
Cardinal Clinical Features of PD

- Bradykinesia or slowness
- Rigidity or stiffness
- Tremor
- Gait disturbance
Hallmark Neuropathologic Features of Parkinson’s Disease

- Substantia Nigra pars compacta neuronal loss
- Reduced striatal dopamine
- Lewy bodies and Lewy neurites
Sites of Neurodegeneration and Lewy Pathology in PD

- Substantia nigra pars compacta – **Dopamine neurons**
- Locus coeruleus – **Norepinephrine neurons**
- Nucleus basalis of Meynert – **Cholinergic neurons**
- Dorsal Raphe – **Serotonin neurons**
- Cerebral cortex
- Olfactory system
- Pedunculopontine nucleus
- Dorsal motor nucleus of the Vagus
- Spinal cord
- Peripheral autonomic nervous system
Non-Dopaminergic Features of Parkinson’s Disease

- Motor disturbance
  - Freezing
  - Postural instability
  - Falling
  - Dysphagia
- Autonomic dysfunction
  - OH, GI, GU, sexual
- Sensory alterations
- Sleep disturbances
- Mood disorders
- Cognitive impairment
- Dementia
Current Therapy for Parkinson’s Disease

- Primarily based on a dopamine replacement strategy
  - Levodopa
  - Dopamine agonists
  - COMT inhibitors
  - MAO-B inhibitors
- Effective for treatment of the dopaminergic features of PD
- Has provided benefit for millions of PD patients around the world
Limitations of Current Therapy for Parkinson’s Disease

- Side effects
  - Levodopa – motor complications
  - Dopamine Agonists - Sedation, impulse control disorders, peripheral swelling
  - COMT Inhibitors - diarrhea, hepatotoxicity
- Do not adequately control the non-dopaminergic features of PD
- Do not prevent clinical progression
- Do not prevent the development of disability
A Therapy that Slows Clinical Progression is the Major Unmet Medical Need in PD

- A treatment intervention that slows, stops or reverses clinical progression, and prevents or limits the development of cumulative disability
  - Neuroprotection
  - Disease Modifying
  - Slowing Clinical Progression
Obstacles to Developing a Therapy That Slows Clinical Progression in PD

- Uncertainty as to etiology and pathogenesis of Parkinson's Disease
- Lack of an animal model that replicates all of the features of Parkinson's Disease
- Clinical trial design or biomarker that permits an accurate determination of the effect of a study intervention on clinical progression
The DATATOP Study
Time to Disease Milestone

Probability of Reaching End Point

Days After Randomization

PP = Placebo, Placebo
TP = Tocopherol, Placebo
DP = Deprenyl, Placebo
DT = Deprenyl, Tocopherol

P < 0.0001

PSG, NEJM 1993
Endpoints/Designs Used to Date to Measure Clinical Progression

- Time to a milestone of clinical progression
- Neuro-imaging biomarkers of dopaminergic function
- Washout studies
- Change in UPDRS from baseline
Unified Parkinson Disease Rating Scale (UPDRS)

- I – Mentation (4 items)
- II – Activities of Daily Living (13 items)
- III – Motor Examination (27 items)

Each item rated on a 5-point scale
0 = no disability; 4 = maximum disability
Unified Parkinson Disease Rating Scale (UPDRS – Part I)

Mentation
- Intellectual impairment
- Thought disorder
- Depression
- Motivation/initiative
Unified Parkinson Disease Rating Scale (UPDRS – Part II)

Daily Living Activities

- Speech
- Salivation
- Swallowing
- Handwriting
- Cutting food
- Dressing
- Hygiene
- Turning in bed
- Falling
- Freezing
- Walking
- Tremor
- Sensory Complaints
Unified Parkinson Disease Rating Scale (UPDRS – Part III)

**Motor**

- Speech
- Facial expression
- Tremor at rest
- Postural tremor
- Rigidity
- Finger taps
- Hand movements
- Rapid movements
- Leg agility
- Arising from chair
- Posture
- Gait
- Postural stability
- Body bradykinesia
Using UPDRS Rate of Decline to Identify Effect of a Drug on Clinical Progression

Bhattaram et al. AAPS J 2009
Trial Designs to Assess Clinical Progression in PD

- Randomized Withdrawal
- Delayed Start Design
Delayed-start Design

Period I

Placebo

Early-start

Early Intervention
Delayed-start Design
Symptomatic Effect

Period I

Placebo

Early-start

Early Intervention

Delayed-start

Period II

Delayed Intervention

Consistent with Disease Modifying Effect
Delayed-start Design
Slowing Clinical Progression

Period I

Placebo

Early-start

Early Intervention

Period II

Delayed-start

Consistent with Disease Modifying Effect

Delayed Intervention
Delayed-start Design Study Issues

- Period I – must be long enough to show slowing of clinical progression
- Period II – must be long enough for full symptomatic effect to occur
- Periods I and II – must not be so long that patients withdraw because they need additional therapy
- Must be sufficient numbers of visits in periods I and II to calculate rate of UPDRS deterioration (slope)
- Drop outs must be minimized
- Missing data must be addressed prospectively with pre-defined sensitivity and imputation analyses
Delayed-start Design Patient Issues

- Early patients
  - Better chance of obtaining disease modifying effect
  - Low risk of drop out
  - Slow rate of progression – harder to see benefit

- More advanced patients
  - Faster rate of progression – easier to see benefit
  - Greater risk of drop outs
  - May be too late to obtain an effect that slows clinical progression
Delayed-start Design Analysis Issues

I. Superiority of Early Start vs Placebo

II. Superiority of Early Start vs Delayed Start

III. Non-Inferiority of Early Start vs Delayed Start

Mean UPDRS change from baseline

Week

Delayed Start (Placebo-Active)
Early Start (Active-Active)

Olanow et al. Mov Disord. 2008
Summary

- PD patients experience disability not adequately controlled with available medical and surgical therapies
- Slowing clinical progression is important unmet need
- Previous clinical trial designs cannot differentiate slowing progression from symptomatic effects
- Delayed start design permits distinguishing between symptomatic effect and slowing clinical progression
Efficacy and Safety of Rasagiline TEMPO and ADAGIO

Cheryl Fitzer-Attas, Ph.D.
Director of Scientific and Medical Affairs
Teva Pharmaceuticals
Rasagiline Mesylate
N-propargyl-1(R)-aminooindan Mesylate

- MAO-B Inhibitor that incorporates a propargylamine structure
**Rasagiline is Protective in Laboratory Models: In Vitro Models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Insult</th>
<th>Cytotoxic mechanism</th>
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<tbody>
<tr>
<td>SH-SY5Y cells</td>
<td>NM(R)Sal</td>
<td>Intrinsic apoptosis</td>
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<tr>
<td>SH-SY5Y cells</td>
<td>Sin-1 (peroxynitrite-generating agent)</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>SH-SY5Y cells</td>
<td>6-OHDA</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>PC12 cells</td>
<td>Ischemia</td>
<td>Oxidative stress</td>
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<tr>
<td>Cerebellar granule cells</td>
<td>Serum withdrawal</td>
<td>Apoptosis</td>
</tr>
<tr>
<td>SK-N-SH cells</td>
<td>High-density culture</td>
<td>Apoptosis</td>
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</tbody>
</table>

Adapted from Naoi & Maruyama. Exp Rev Neurother 2009. 9 (8):1233
## Rasagiline is Protective in Laboratory Models: Animal Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Insult</th>
<th>Cytotoxic mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monkey</td>
<td>MPTP</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Rat</td>
<td>Ischemia</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Rat</td>
<td>SHP</td>
<td>Aging</td>
</tr>
<tr>
<td>Rat</td>
<td>Thiamine deficiency</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Rat</td>
<td>6-OHDA</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Mouse</td>
<td>MPTP</td>
<td>Neurotoxin</td>
</tr>
<tr>
<td>Mouse</td>
<td>Lactacystin</td>
<td>UPS inhibition</td>
</tr>
<tr>
<td>Mouse</td>
<td>3-NP (MSA model)</td>
<td>α-synuclein</td>
</tr>
<tr>
<td>Rat</td>
<td>6-OHDA and lactacystin</td>
<td>Oxidative stress and UPS inhibition</td>
</tr>
</tbody>
</table>

Adapted from Naoi & Maruyama. Exp Rev Neurother 2009. 9 (6):1233
TEMPO Study Objectives
(TVP-1012 in Early Monotherapy for Parkinson’s Disease Outpatients)

- **Main objective:** Evaluate the safety and efficacy of rasagiline monotherapy in patients with early PD
- **Pre-specified, exploratory objective:** Compare the effects of early versus delayed initiation of rasagiline on clinical progression in patients with PD

PSG. Arch Neurol 2002; 59: 1937; PSG. Arch Neurol 2004; 61: 561
TEMPO Employed a Delayed-start Design

Subjects were randomized in the USA and Canada

Randomization 1:1:1

Weeks

0 26 52

Double-blind, placebo-controlled phase n=404

Double-blind, active-treatment phase n=380

n=134

n=132

n=138

PSG. Arch Neurol 2002; 59: 1937; PSG. Arch Neurol 2004; 61: 561
TEMPO: Designed to Recruit an Early and Mild PD Population

- Age >35 years
- Early idiopathic PD
- PD confirmed by presence of ≥2 cardinal signs
  - Resting tremor
  - Rigidity
  - Bradykinesia
- Hoehn & Yahr stage ≤3
TEMPO: Additional Parkinsonian Therapy Allowed in Active Phase

- Placebo-controlled phase
  - Only stable doses of anticholinergic medication allowed
  - If investigator determined subject needed additional anti-PD therapy, subject proceeded to the active-treatment phase

- Active-treatment phase
  - Additional anti-PD therapy allowed
  - Efficacy analysis excluded these measurements

TEMPO: Relatively Low (10.9%) Dropout Over the Course of Placebo and Active Control Phases

404 Subjects Randomized ITT

- 54 Early transfer
  - Delayed-start - 21 (15.2%)
  - Early-start 1mg - 14 (10.4%)
  - Early-start 2mg - 19 (14.4%)

24 (5.9%) Withdrawals
- Adverse event - 8
- Failed to return - 1
- Subject request - 7
  - Unsatisfactory response - 3
  - Protocol violation - 1
  - Other - 4

380 (94.1%) Entered Active-Treatment Phase

20 (5.0%) Withdrawals
- Adverse event - 5
- Subject request - 9
  - Unsatisfactory response - 1
  - Other - 5

360 (89.1%) Completed Study
TEMPO: Similar Baseline Characteristics Across Groups

<table>
<thead>
<tr>
<th></th>
<th>Rasagiline 1mg early-start</th>
<th>Rasagiline 2mg early-start</th>
<th>Rasagiline 2mg delayed-start</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized (n)</td>
<td>134</td>
<td>132</td>
<td>138</td>
<td>404</td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>61.6 (10.3)</td>
<td>60.4 (11.4)</td>
<td>60.5 (10.8)</td>
<td>60.8 (10.8)</td>
</tr>
<tr>
<td>Male patients (n, %)</td>
<td>90 (67.2)</td>
<td>74 (56.1)</td>
<td>93 (67.4)</td>
<td>257 (63.6)</td>
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<tr>
<td>PD duration, years</td>
<td>11.1 (14.9)</td>
<td>13.9 (15.8)</td>
<td>11.3 (13.2)</td>
<td>12.1 (14.7)</td>
</tr>
<tr>
<td>(mean, SD)</td>
<td></td>
<td></td>
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<tr>
<td>UPDRS – Total score</td>
<td>24.7 (11.3)</td>
<td>25.9 (9.5)</td>
<td>24.5 (11.6)</td>
<td>25.0 (10.8)</td>
</tr>
<tr>
<td>(mean, SD)</td>
<td></td>
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<tr>
<td>Hoehn &amp; Yahr (mean, SD)</td>
<td>1.9 (0.5)</td>
<td>1.9 (0.5)</td>
<td>1.9 (0.5)</td>
<td>1.9 (0.5)</td>
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TEMPO Efficacy Cohort Included 91.8% of Active-Treatment Phase

<table>
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<th>Rasagiline 1mg early-start</th>
<th>Rasagiline 2mg early-start</th>
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<tr>
<td>Randomized</td>
<td>134</td>
<td>132</td>
<td>138</td>
<td>404</td>
</tr>
<tr>
<td>Entered active-treatment phase</td>
<td>124</td>
<td>124</td>
<td>132</td>
<td>380</td>
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<tr>
<td>Efficacy Analysis of active-treatment phase*</td>
<td>122</td>
<td>119</td>
<td>130</td>
<td>371</td>
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</table>

*at least 1 UPDRS measurement in the active phase without additional anti-PD therapy
TEMPO: 52 Week Analysis Used for Slowing of Clinical Progression Assessment

Superiority of early-start vs delayed-start at study end (mean UPDRS change from baseline to termination using ANCOVA)
Are UPDRS changes different?

Schematic illustration
TEMPO: Early-start Rasagiline 1mg Provides Better Clinical Outcome than Delayed-start

- Delayed-start (placebo–rasagiline 2mg)
- Early-start (rasagiline 1mg)

Mean UPDRS change from baseline

Week

1.8
p=0.05

TEMPO: Early-start Rasagiline 2mg Provides Better Clinical Outcome than Delayed-start

- Delayed-start (placebo–rasagiline 2mg)
- Early-start (rasagiline 2mg)

Mean UPDRS change from baseline

Week

P=0.01

2.3

PSG. Arch Neurol 2002; 59: 1937; PSG. Arch Neurol 2004; 61: 561
TEMPO: Differences Cannot be Fully Explained by Rasagiline’s Symptomatic Effects

A Controlled, Randomized, Delayed-Start Study of Rasagiline in Early Parkinson Disease

Parkinson Study Group

Arch Neurol 2004; 61: 561–566

- “… the differences in performance observed at the final visit cannot be fully explained by the symptomatic effects of rasagiline…”

- One potential explanation of our results is that rasagiline slows the progression of disability of PD.”
TEMPO Long-term: Patients Took Rasagiline 1mg & Additional Parkinsonian Medication

Randomization 1:1:1

Rasagiline 1mg

Rasagiline 2mg

Placebo

Rasagiline 2mg

Rasagiline 1mg

Years

0

1

6

TEMPO n=404

//

TEMPO extension n=306

Blinded for initial randomization
TEMPO Long-term: the Benefit of Early-start Rasagiline is Maintained Over 6 Years

Overall difference between early and delayed-start groups is 16%, p=0.006

Data points for 6 and 6.5 years are combined; Hauser, et al. Mov Disord 2009; 24: 564-73
Main Objective: Investigate the effect of rasagiline on clinical progression of Parkinson’s disease
ADAGIO: Designed to Assess Effects on Slowing of Clinical Progression

Early PD patients not using any anti-PD medication

Randomization 1:1:1:1

Rasagiline 1mg

n=288

Placebo

Rasagiline 1mg

n=300

Rasagiline 2mg

n=295

Rasagiline 2mg

n=293

Visit (week)

-4 0 12 24 36 42 48 54 60 66 72

36-week double-blind placebo-controlled phase
n=1,176

36-week double-blind active-treatment phase
n=1,091

ADAGIO: Designed to Recruit an Early and Mild Parkinson’s Disease Population

- Inclusion criteria
  - Idiopathic PD confirmed by presence of ≥2 cardinal signs
  - Hoehn & Yahr stage <3
  - Diagnosis of PD <1.5 years
  - Untreated PD judged not to require symptomatic therapy for 9 months

- Exclusion criteria
  - Patients with atypical or secondary parkinsonism
  - Previous use of anti-parkinsonian agents for >3 weeks

ADAGIO: No Other Parkinsonian Therapy was Allowed

- Placebo-controlled phase
  - If investigator determined subject needed additional anti-PD therapy, subject proceeded to the active-treatment phase

- Active-treatment phase
  - If investigator determined subject needed additional anti-PD therapy, subject was prematurely withdrawn from the study

ADAGIO: Relatively Low (18.9%) Dropout Over the Course of Placebo and Active Control Phases

1176 Subjects Randomized (ITT)

177 Early transfer
- Delayed Start - 118 (19.8%)
- Early Start - 59 (10.2%)

1091 (92.7%) entered Active Treatment

85 (7.2%) Withdrawals
- Adverse event - 37
- Withdrew consent - 23
- Needed treatment - 16
- Other reasons - 9

137 (11.6%) Withdrawals
- Needed treatment - 99
- Withdrew consent - 14
- Adverse event - 17
- Other reasons - 7

954 (81.1%) Completed study
Evolution of ADAGIO Study Design and Analyses
ADAGIO: Original 2 Endpoints Required to Show Slowing of Clinical Progression

Superiority of Early-start vs Delayed-start
(mean UPDRS change from baseline across Week 48-72)
Are UPDRS changes different?

Non-inferiority of slopes in active-treatment phase
(Weeks 48–72: margin of 0.15)
Are curves non-convergent?

Schematic illustration
ADAGIO: 3 Hierarchical Endpoints Required to Show Slowing of Clinical Progression

Superiority of slopes in placebo-controlled phase (Weeks 12–36)
Are curves divergent?

Superiority of Early-start vs Delayed-start at study end (mean UPDRS change from baseline to Week 72)
Are changes different?

Non-inferiority of slopes in active-treatment phase (Weeks 48–72; margin of 0.15)
Are curves non-convergent?

ADAGIO: Modified ITT and ACTE Cohorts were Defined for the Primary Endpoints

Modified ITT
UPDRS measurements at baseline and from week 12

ITT
All subjects randomized

Week 0 12 24 36 42 48 54 60 66 72

ACTE (ACTive Efficacy)
At least 24 weeks in PC phase
At least one UPDRS measurement after 12 weeks in the active phase
ADAGIO: Modified ITT and ACTE Cohorts were Defined for the Primary Endpoints

ITT
N=1176

Modified ITT
N=1164
Endpoint I

Week
0  12  24  36  42  48  54  60  66  72

ACTE (ACTive Efficacy)
N=996
Endpoints II and III
**ADAGIO: Similar Baseline Characteristics Across Groups, All with Early and Mild PD**

<table>
<thead>
<tr>
<th></th>
<th>Rasagiline 1mg delayed-start</th>
<th>Rasagiline 1mg early-start</th>
<th>Rasagiline 2mg delayed-start</th>
<th>Rasagiline 2mg early-start</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>300</td>
<td>288</td>
<td>295</td>
<td>293</td>
<td>1,176</td>
</tr>
<tr>
<td>Age, yrs (mean, SD)</td>
<td>61.9 (9.7)</td>
<td>62.4 (9.7)</td>
<td>62.4 (9.7)</td>
<td>62.3 (9.6)</td>
<td>62.2 (9.7)</td>
</tr>
<tr>
<td>Male patients (n, %)</td>
<td>186 (62.0)</td>
<td>175 (60.8)</td>
<td>182 (61.7)</td>
<td>175 (59.7)</td>
<td>718 (61.1)</td>
</tr>
<tr>
<td>PD duration, months (mean, SD)</td>
<td>4.3 (4.6)</td>
<td>4.6 (4.7)</td>
<td>4.6 (4.6)</td>
<td>4.6 (4.6)</td>
<td>4.5 (4.6)</td>
</tr>
<tr>
<td>UPDRS total score (mean, SD)</td>
<td>20.2 (8.8)</td>
<td>20.6 (8.4)</td>
<td>19.9 (8.1)</td>
<td>20.8 (8.8)</td>
<td>20.4 (8.5)</td>
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<td>Hoehn &amp; Yahr (mean, SD)</td>
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**ADAGIO: Similar Baseline Characteristics Between ITT, Modified ITT, and ACTE Cohorts**

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<th></th>
<th>ITT</th>
<th>mITT</th>
<th>ACTE</th>
</tr>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>1176</td>
<td>1164</td>
<td>996</td>
</tr>
<tr>
<td>Male patients (n, %)</td>
<td>718 (61.1)</td>
<td>709 (60.9)</td>
<td>603 (60.5)</td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>62.2 (9.6)</td>
<td>62.2 (9.6)</td>
<td>62.4 (9.4)</td>
</tr>
<tr>
<td>PD duration, months (mean, SD)</td>
<td>4.5 (4.6)</td>
<td>4.5 (4.6)</td>
<td>4.6 (4.6)</td>
</tr>
<tr>
<td>UPDRS total score (mean, SD)</td>
<td>20.4 (8.5)</td>
<td>20.4 (8.5)</td>
<td>19.8 (8.2)</td>
</tr>
<tr>
<td>Modified Hoehn &amp; Yahr (mean, SD)</td>
<td>1.5 (0.5)</td>
<td>1.5 (0.5)</td>
<td>1.5 (0.5)</td>
</tr>
</tbody>
</table>
### ADAGIO: ACTE Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rasagiline 1mg delayed-start</th>
<th>Rasagiline 1mg early-start</th>
<th>Rasagiline 2mg delayed-start</th>
<th>Rasagiline 2mg early-start</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>238</td>
<td>251</td>
<td>249</td>
<td>258</td>
<td>996</td>
</tr>
<tr>
<td>Age, yrs (mean, SD)</td>
<td>62.2 (9.2)</td>
<td>62.9 (9.5)</td>
<td>62.5 (9.3)</td>
<td>62.2 (9.8)</td>
<td>62.4 (9.4)</td>
</tr>
<tr>
<td>Male patients (n, %)</td>
<td>147 (61.8)</td>
<td>153 (61.0)</td>
<td>152 (61.0)</td>
<td>151 (58.5)</td>
<td>603 (60.5)</td>
</tr>
<tr>
<td>PD duration, months (mean, SD)</td>
<td>4.5 (4.7)</td>
<td>4.8 (4.8)</td>
<td>4.5 (4.5)</td>
<td>4.5 (4.4)</td>
<td>4.6 (4.6)</td>
</tr>
<tr>
<td>UPDRS total score (mean, SD)</td>
<td>19.10 (8.07)</td>
<td>20.53 (8.45)</td>
<td>19.24 (7.87)</td>
<td>20.27 (8.45)</td>
<td>19.80 (8.23)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr (mean, SD)</td>
<td>1.50 (0.49)</td>
<td>1.52 (0.49)</td>
<td>1.44 (0.47)</td>
<td>1.50 (0.49)</td>
<td>1.49 (0.48)</td>
</tr>
</tbody>
</table>
ADAGIO: Rasagiline 1mg Observed Data for Modified ITT Cohort (Weeks 0-36)
ADAGIO: Rasagiline 1mg Observed Data for Modified ITT Cohort (Weeks 0-36)

Mean UPDRS change from baseline

Worsening

Improvement

Week

Difference between slopes
-0.046 units/week
(-2.4 units/year)

Delayed (n) 593 588 549 485
Early (n) 288 286 276 259

0.139 (7.2)
0.093 (4.8)
ADAGIO: Rasagiline 1mg Observed Data for ACTE Cohort (Weeks 0-72)

ADAGIO: Discovery of Covariate Effects in SAP Combined Data Set Analysis

- Initial assumption that two covariate effects would be similar for 1 and 2mg components
  - Baseline UPDRS and treatment center
- However, interactions found in the data
  - Baseline UPDRS ($p=0.0481$)
  - Treatment center ($p=0.0125$)
- 1mg and 2mg data were analyzed as separate data sets
A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson’s Disease

C. Warren Olanow, M.D., Olivier Rascol, M.D., Ph.D., Robert Hauser, M.D., Paul D. Feigin, Ph.D., Joseph Jankovic, M.D., Anthony Lang, M.D., William Langston, M.D., Eldad Melamed, M.D., Werner Poewe, M.D., Fabrizio Stocchi, M.D., and Eduardo Tolosa, M.D., for the ADAGIO Study Investigators*
ADAGIO Results: 1mg Dose Endpoint II

<table>
<thead>
<tr>
<th></th>
<th>Final SAP Week 72 only combined data set</th>
<th>Alternative Week 72 only separate data sets</th>
<th>Original SAP Weeks 48-72 combined data set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-Start (Week 72)</td>
<td>-1.4</td>
<td>-1.7</td>
<td>-1.4</td>
</tr>
<tr>
<td>Delayed-start (Week 72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(UPDRS units)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.051</td>
<td>0.025</td>
<td>0.012</td>
</tr>
</tbody>
</table>

For primary analysis, $\alpha=0.025$
## ADAGIO Results: 1mg Dose Endpoint III

<table>
<thead>
<tr>
<th></th>
<th>Final SAP Week 72 only Combined Data Set</th>
<th>Alternative Week 72 only Separate Data Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope (<em>{(\text{Delayed-Start})}) - Slope (</em>{(\text{Early-Start})}) (\text{(UPDRS-Total Units/Week)})</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Upper Limit of 90% CI</td>
<td>0.027</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Required Criteria for Upper Limit of 90% CI = 0.15
ADAGIO Alternative Analysis: Results Support Disease Modifying Effect of Rasagiline

Slope_{(rasagiline)} – slope_{(placebo)} = -0.05, p=0.0133; 95% CI: -0.08, -0.01
Curves are divergent

Week 72_{(early-start)} – Week 72_{(delayed-start)} = -1.7, p=0.025; 95% CI: -3.15, -0.21
UPDRS changes are different

Slope_{(early-start)} – slope_{(delayed-start)} = -0.0, 90% CI: -0.04, 0.04
Curves are non-convergent


Schematic illustration
Delayed-start Design Study Issues

- Period I – must be long enough to show slowing of clinical progression
- Period II – must be long enough for full symptomatic effect to occur
- Periods I and II – must not be so long that patients withdraw because they need additional therapy
- Must be sufficient numbers of visits in periods I and II to calculate rate of UPDRS deterioration (slope)
- Drop outs must be minimized
- Missing data must be addressed prospectively with pre-defined sensitivity and imputation analyses
ADAGIO: Consistent Results Demonstrated for 1mg Dose in Endpoint I
ADAGIO: Consistent Results Demonstrated for 1mg Dose in Endpoint II

Change From Baseline to Week 72 in UPDRS-Total Score

- ACTE
  - Imputed ITT*: p=0.0250
  - ITT (Observed Data): p=0.0295
  - ACTE: p=0.0249
  - Imputed ITT*: p=0.0422
- Completers*: p=0.0374
- Per Protocol: p=0.0392
- ACTE: p=0.0119

*Predefined sensitivity analysis
ADAGIO: Consistent Results Demonstrated for 1 mg Dose in Endpoint III

Changes Per Week (Slopes) in UPDRS-Total Score
ADAGIO: Rasagiline 1mg Dose Results Support Slowing of Clinical Progression

- Results from three primary endpoints support slowing of clinical progression
- Further supported by various imputation strategies and sensitivity analyses for all endpoints
ADAGIO 2mg
ADAGIO: Rasagiline 2mg Observed Data for Modified ITT Cohort (Weeks 0-36)

Week 0-36:
- Placebo: 12, 1.2, 2.3, 3.6, 4.5
- Rasagiline 2mg: -0.5, -0.8, -1.2, -2, -3

Means of UPDRS change from baseline:
- Delayed (n): 593, 588, 549, 485
- Early (n): 293, 289, 280, 260
ADAGIO: Rasagiline 2mg Observed Data for Modified ITT Cohort (Weeks 0-36)

Mean UPDRS change from baseline

Worsening

Improvement

Delay (n) 593 588 549 485
Early (n) 293 289 280 260

Difference between slopes
-0.072 units/week
(-3.7 units/year)

Week
ADAGIO: Rasagiline 2mg Observed Data for ACTE Cohort (Weeks 0-72)

Mean UPDRS change from baseline

- Delayed-start (placebo–rasagiline 2mg)
- Early-start (rasagiline 2mg)

Improvement
Worsening

Week

Delayed (n)
Early (n)

249
258
249
257
249
258
235
253
249
256
249
256
241
246
238
235
229

237

ADAGIO: Rasagiline 2mg Dose Did Not Meet Endpoint II

Slope_{rasagiline} - slope_{placebo} = -0.07, p<0.001; 95% CI: -0.11, -0.04
Curves are divergent

Week 72_{early-start} - Week 72_{delayed-start} = 0.36, p=0.603
Changes are not different

Possible Explanations for ADAGIO 2mg Results on Endpoint II

- Chance
- Different pharmacology
- Impact of early transfers
- Lower sensitivity to detect change in UPDRS scale in milder patients
Patients at Baseline More Advanced in TEMPO than in ADAGIO

<table>
<thead>
<tr>
<th></th>
<th>TEMPO</th>
<th>ADAGIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized (n)</td>
<td>404</td>
<td>1,176</td>
</tr>
<tr>
<td>Male patients (n, %)</td>
<td>257 (63.6%)</td>
<td>718 (61.1%)</td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>60.8 (10.8)</td>
<td>62.2 (9.6)</td>
</tr>
<tr>
<td>PD duration, months (mean, SD)</td>
<td>12.1 (13.2)</td>
<td>4.5 (4.6)</td>
</tr>
<tr>
<td>UPDRS-Total score (mean, SD)</td>
<td>25.0 (10.8)</td>
<td>20.4 (8.5)</td>
</tr>
<tr>
<td>UPDRS-Motor score (mean, SD)</td>
<td>17.8 (8.43)</td>
<td>14.2 (6.4)</td>
</tr>
<tr>
<td>Modified Hoehn &amp; Yahr (mean, SD)</td>
<td>1.9 (0.5)</td>
<td>1.5 (0.5)</td>
</tr>
</tbody>
</table>
ADAGIO: Rasagiline 2mg Was Assessed in Subjects with Highest BL UPDRS Scores

- A post-hoc analysis was conducted in subjects with highest baseline Total-UPDRS scores (>25.5)

ADAGIO: Highest Baseline UPDRS Scores (>25.5) – Rasagiline 2 mg

ADAGIO 2mg: Results in Subjects with Highest Baseline UPDRS Scores

- **Slope (rasagiline) - slope (placebo) = -0.20, p<0.001; 95% CI: -0.30, -0.11**

- **Week 72 (early-start) - Week 72 (delayed-start) = -3.63, p=0.04; 95% CI: -7.04, -0.21**

- **Slope (early-start) - slope (delayed-start) = -0.03; 90% CI: -0.13, 0.06**


Schematic illustration
ADAGIO: Rates of UPDRS Progression for Placebo Subjects

Placebo subjects >25.5 slope = 0.244 (13 UPDRS units/year)

Placebo (all patients) slope = 0.139 (7 UPDRS units/year)

Rascol et al. Lancet Neurol. 2011 May;10(5):415
Safety Rasagiline

1mg and 2mg
Patient Exposure to Rasagiline

- Patient-years of exposure to rasagiline in early and late PD
  - Clinical trials: >4,500 patient-years
  - Post-marketing: >500,000 patient-years
- Label reflects information from all these patients
**ADAGIO: Rasagiline Safety Profile Similar to Placebo**

<table>
<thead>
<tr>
<th>Placebo-controlled Phase</th>
<th>Placebo (n=593) %</th>
<th>Rasagiline 1mg (n=288) %</th>
<th>Rasagiline 2mg (n=293) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of AEs</td>
<td>68.0</td>
<td>65.3</td>
<td>68.3</td>
</tr>
<tr>
<td>Incidence of SAEs</td>
<td>3.7</td>
<td>4.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Discontinuations associated with AEs</td>
<td>2.9</td>
<td>3.1</td>
<td>3.4</td>
</tr>
</tbody>
</table>
### ADAGIO: No Apparent Relationship Between Dose and Rate of Adverse Events

<table>
<thead>
<tr>
<th>Placebo-controlled Phase</th>
<th>Placebo (n=593) %</th>
<th>Rasagiline 1mg (n=288) %</th>
<th>Rasagiline 2mg (n=293) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>2.9</td>
<td>5.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.2</td>
<td>4.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.0</td>
<td>3.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.2</td>
<td>3.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Fall</td>
<td>3.9</td>
<td>3.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>3.4</td>
<td>2.1</td>
<td>4.4</td>
</tr>
</tbody>
</table>
### ADAGIO: Dopaminergic AEs Similar in Rasagiline and Placebo

<table>
<thead>
<tr>
<th>Placebo-controlled Phase</th>
<th>Placebo (n=593)</th>
<th>Rasagiline 1mg (n=288)</th>
<th>Rasagiline 2mg (n=293)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>3.9%</td>
<td>4.2%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.9%</td>
<td>1.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.5%</td>
<td>0.7%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>0.8%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hallucination</td>
<td>0.2%</td>
<td>-</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>-</td>
<td>-</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
ADAGIO: Safety and Tolerability
Selected Safety Issues

- Melanoma
  - One case of in-situ melanoma at week 72

- Serotonin syndrome
  - 196 (17.4%) subjects on rasagiline on antidepressants
  - No reports of a serotonin syndrome

- Tyramine effect
  - No restriction on dietary tyramine intake
  - No reports of a tyramine reaction

Good Safety Profile for Rasagiline

- ADAGIO safety profile for rasagiline similar to placebo
  - Overall AEs
  - SAEs
  - Dopaminergic AEs
  - Selected safety issues not a concern
Results of Two Trials Support Expanded Indication for Rasagiline

- TEMPO and ADAGIO independently substantiate effectiveness of rasagiline

- Favorable safety profile of rasagiline, reflected in current label
Interpreting The Rasagiline Delayed-Start Studies

C. Warren Olanow, M.D.
Henry P. and Georgette Goldschmidt Professor and Chairman Emeritus, Department of Neurology Professor, Department of Neuroscience Director, Robert and John M. Bendheim Parkinson’s Disease Center Mount Sinai School of Medicine
The ADAGIO Study Publication

A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson’s Disease

C. Warren Olanow, M.D., Olivier Rascol, M.D., Ph.D., Robert Hauser, M.D., Paul D. Feigin, Ph.D., Joseph Jankovic, M.D., Anthony Lang, M.D., William Langston, M.D., Eldad Melamed, M.D., Werner Poewe, M.D., Fabrizio Stocchi, M.D., and Eduardo Tolosa, M.D., for the ADAGIO Study Investigators*
ADAGIO Delayed Start Study Methodology

Endpoints and Analyses to Discern Disease-Modifying Drug Effects in Early Parkinson’s Disease

Venkatesh Atul Bhattaram,1 Ohidul Siddiqui,2 Leonard P. Kapraun,3 and Jogarao V. S. Gobburu1,4

Received 8 December 2009; accepted 27 May 2009; published online 12 June 2009

Abstract. Parkinson’s disease is an age-related degenerative disorder of the central nervous system that often impairs the sufferer’s motor skills and speech, as well as other functions. Symptoms can include tremor, stiffness, slowness of movement, and impaired balance. An estimated 4 million people worldwide suffer from the disease, which usually affects people over the age of 60. Presently, there is no precedent for approving any drug as having a modifying effect (i.e., slowing or delaying) for disease progression of Parkinson’s disease. Clinical trial designs such as delayed start and withdrawal are being proposed to discern symptomatic and protective effects. The current work focused on understanding the futures of delayed start design using prior knowledge from published and data submitted to US Food and Drug Administration (US FDA) as part of drug approval or protocol evaluation. Clinical trial simulations were conducted to evaluate the false-positive rate, power under a new statistical analysis methodology, and various scenarios leading to patient discontinuations from clinical trials. The outcome of this work is part of the ongoing discussion between the US FDA and the pharmaceutical industry on the standards required for demonstrating disease-modifying effect using delayed start design.

KEY WORDS: delayed start; disease modification; neuroprotection; Parkinson’s disease; randomized start.

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,1,8 Robert Hauser, MD,2 Joseph Jankovic, MD,3 William Langston, MD,3 Anthony Lang, MD,1 Werner Pfeewe, MD,1 Edvardanto Tolosa, MD,1 Fabrizio Stocchi, MD,1 Edad Melamed, MD,2 Eli Eyal, PhD,10 and Olivier Rascol, MD11

1Department of Neurology, Mount Sinai School of Medicine, New York, New York, USA
2Parkinson’s Disease and Movement Disorders Center, University of South Florida, Tampa, Florida, USA
3Department of Neurology, Baylor College of Medicine, Houston, Texas, USA
4The Parkinson’s Institute, Sunnyvale, California, USA
5Department of Neurology, Toronto Western Hospital, Toronto, Ontario, Canada
6Department of Neurology, Innsbruck Medical University, Innsbruck, Austria
7Movement Disorder Unit, Neurology Service, Hospital Clinic, University of Barcelona, Spain
8Institute of Neurology, IRCSS San Raffaele Pisana, Rome, Italy
9Department of Neurology, Ranil Medical Center, Bollinom campus, Petah Tikva and Sackler, School of Medicine, Tel Aviv University, Israel
10Global Statistics Unit, Teva Pharmaceuticals Industries Ltd, Israel
11INSERM U145, 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 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 randomized trial (the ADAGIO study). We here describe the rationale for the study and baseline characteristics 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
ADAGIO Study
Rasagiline 1mg

Olanow et al. NEJM; 2009
Positive Delayed Start Study
FDA Model vs ADAGIO - Rasagiline 1mg

Randomized Start Design

Phase I  Phase II
Neuroprotective Effect

Placebo

Early study intervention
Introduction of study to placebo group

A Rasagiline, 1 mg/day

Mean Change in UPDRS Score (points)

Week

Baseline

Bhattaram et al AAPS, 2009
Olanow et al. NEJM; 2009
ADAGIO Study
Rasagiline 2mg

Olanow et al. NEJM; 2009
Rasagiline 2 mg/day
Upper Quartile Analysis

TVP-1012/500 (ADAGIO)
Change in UPDRS (Mean ± SE) — ACTE Data Analysis Set—2mg—Baseline UPDRS GT 25.5

Change in UPDRS

Week

- 2mg Delayed Start
- 2mg Early Start
ADAGIO: Further Results Published in Lancet Neurology

A double-blind, delayed-start trial of rasagiline in Parkinson’s disease (the ADAGIO study): prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes

Olivier Rascol*, Cheryl J Fitz-Attas*, Robert Hauser, Joseph Jankovic, Anthony Lang, J William Langston, Eldad Melamed, Werner Poewe, Fabrizio Stocchi, Eduardo Tolosa, Eli Eyal, Yoni M Weiss, C Warren Olanow*
Breakdown of Physicians Prescribing Medications for PD 2007

Percent writing prescriptions for de novo patients (n=19,673)
- Neurologist: 33.6%
- PCP: 32.8%
- Internist: 19.3%
- Unknown: 14.3%

Percent writing prescriptions for all patients (n=29,682)
- Neurologist: 41.3%
- PCP: 29.3%
- Internist: 16.5%
- Unknown: 13.0%

Rasagiline for Slowing Clinical Progression in Parkinson’s Disease

Teva Pharmaceuticals
PCNSDAC
October 17, 2011
Backup Slides Shown
Significance of the Dose Level Interactions

- Dose level by center interaction: $p=0.0125$
- Dose level by baseline UPDRS interaction: $p=0.0481$
Nature of Dose Level Interactions

- Based on the combined dataset with model including dose-level interactions:
- Baseline UPDRS coefficients for each dose level:
  - 1 mg dose-level coef. (SE): 0.047 (0.036); p=0.19
  - 2 mg dose-level coef. (SE): -0.053 (0.036); p=0.13
- Difference (1mg vs 2mg dose-level): 0.1 (0.05); p=0.048
Relative Contribution of UPDRS-Mental, ADL, and Motor Sub-scores to UPDRS Baseline, and Treatment effects (1mg Rasagiline)

The difference between early- and delayed start treatment was primarily driven by improvements in ADL subscores.

*p<0.05; **p<0.0001; Note that the treatment effect for each subscale has been estimated using separate models.

Separate Dataset 1 mg: Treatment by Center Interaction

ADAGIO - Active Phase - Separated 1mg Data Set
Estimates of Early-Delayed Start within Center (Mean across Visits)
P-Value of Treatment by Center Interaction = 0.001
Circle size is proportional to the number of subjects in each Center
ADAGIO: Rasagiline 1mg Observed Data for ACTE Cohort (Weeks 0-72)

ADAGIO: Rasagiline 1mg Observed Data for ACTE Cohort (Weeks 0-72)

- Delayed-start (placebo–rasagiline 1mg)
- Early-start (rasagiline 1mg)

Mean UPDRS change from baseline

<table>
<thead>
<tr>
<th>Week</th>
<th>Delayed (n)</th>
<th>Early (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>238</td>
<td>251</td>
</tr>
<tr>
<td>12</td>
<td>238</td>
<td>251</td>
</tr>
<tr>
<td>24</td>
<td>238</td>
<td>251</td>
</tr>
<tr>
<td>36</td>
<td>225</td>
<td>246</td>
</tr>
<tr>
<td>42</td>
<td>237</td>
<td>251</td>
</tr>
<tr>
<td>48</td>
<td>238</td>
<td>251</td>
</tr>
<tr>
<td>54</td>
<td>226</td>
<td>242</td>
</tr>
<tr>
<td>60</td>
<td>223</td>
<td>239</td>
</tr>
<tr>
<td>66</td>
<td>218</td>
<td>233</td>
</tr>
<tr>
<td>72</td>
<td>217</td>
<td>230</td>
</tr>
</tbody>
</table>

Worsening

Improvement

p-value 0.093
ADAGIO: Rasagiline 1mg Observed Data for ACTE Cohort (Weeks 0-72)
ADAGIO: Rasagiline 1mg Observed Data for ACTE Cohort (Weeks 0-72)

- Delayed-start (placebo–rasagiline 1mg)
- Early-start (rasagiline 1mg)

Mean UPDRS change from baseline

- Delayed (n) 238 238 238 225 237 238 226 223 218 217
- Early (n) 251 251 251 246 251 251 242 239 233 230

Weeks:
- 12, 24, 36, 42, 48, 54, 60, 66, 72

Values:
- 0.093, 0.085
- 0.071, 0.085

Worsening to Improvement
ADAGIO: Rasagiline 1mg Observed Data for ACTE Cohort (Weeks 0-72)
Figure 7 Change from Baseline in UPDRS during Active Phase (ACTE) for 1MG
PROUD Results

PROUD Study: Adjusted mean change (95% CI) in UPDRS-Total from baseline

- **Delayed-start (n=200)**
  - Placebo–pramipexole 1.5 mg/day

- **Early-start (n=210)**
  - Pramipexole 1.5 mg/day

Schapira et al. Poster at WFN 2009
ADAGIO: Handling of Missing Values

- Primary Analysis
  - ACTE data set
  - Mixed Models Repeated Measures (MMRM)
- Sensitivity Analyses – ACTE data set
  - Regression-based multiple imputation
  - MMRM with propensity score adjustment
    - Attempt to account for non-random exclusion of subjects from the ACTE data set
    - Stratification (quintiles of propensity score)
    - Regression (continuous propensity score)
- MAR assumption for these analyses
ADAGIO: Handling of Missing Values

- Sensitivity Analyses – ITT or mITT data sets
  - MMRM (mITT)
  - Regression-based multiple imputation (ITT)
- MAR assumption for these analyses
- Sensitivity Analyses – "Worst Case"
  - Applied to ACTE and ITT data sets
  - All missing values at a particular visit were replaced by the mean value in the delayed start group at that visit
Treatment Effect for 1mg – Separate Dataset
Adjusting for Treatment by Covariate Interactions

Adjusting for both interactions (baseline UPDRS, Center):

■ The treatment effect at 72 weeks (SE) = -1.51 (0.76), p=0.0480

Adjusting for only interaction (with baseline UPDRS):

■ The treatment effect at 72 weeks (SE) = -1.63 (0.75), p=0.0305
ADAGIO: No Apparent Relationship Between Dose and Rate of Adverse Events

<table>
<thead>
<tr>
<th>ADAGIO PC Phase</th>
<th>Placebo (N=593)</th>
<th>Rasagiline 1 mg (N=288)</th>
<th>Rasagiline 2 mg (N=293)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>2.9%</td>
<td>5.9%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.2%</td>
<td>4.9%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.0%</td>
<td>3.8%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.2%</td>
<td>3.5%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Fall</td>
<td>3.9%</td>
<td>3.1%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>3.4%</td>
<td>2.1%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>