

Rasagiline for Slowing Clinical Progression in Parkinson's Disease

Teva Pharmaceuticals

PCNSDAC

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Rasagiline for Slowing Clinical Progression in Parkinson's Disease

Dennis Ahern

CNS Therapeutic Area Regulatory Lead
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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 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

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Slowing Clinical Progression in Parkinson's Disease

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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

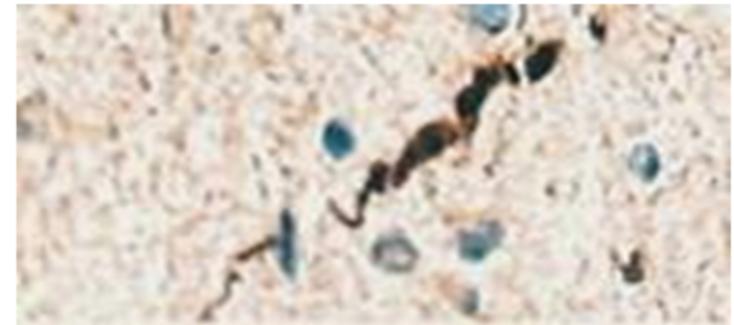
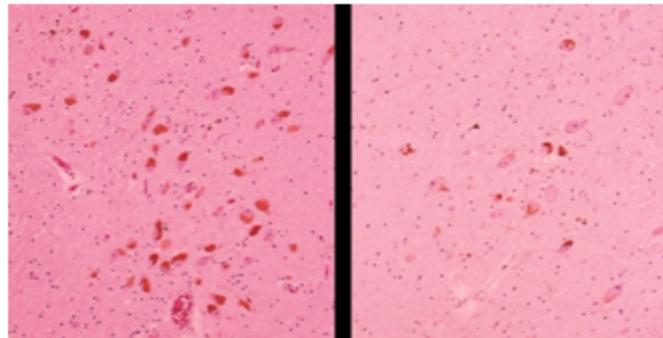
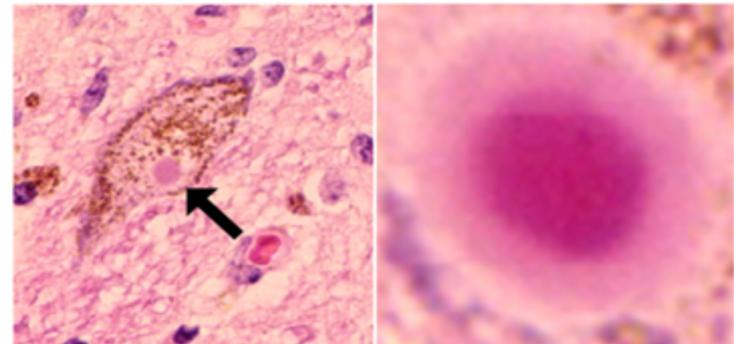
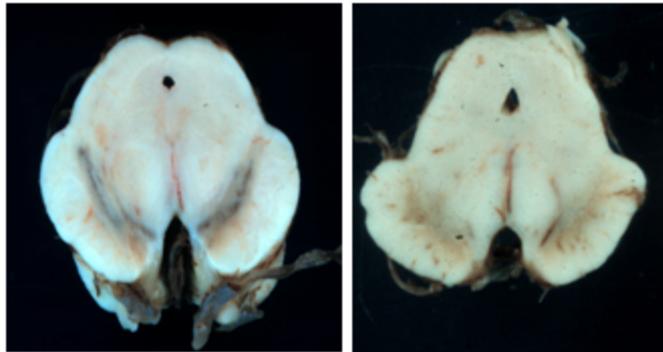
- Age-related neurodegenerative disorder (age of onset at ~60 years)
- Affects ~500,000 - 750,000 persons in United States
- Affects men and women of all races and all occupations
- Frequency expected to dramatically increase in the next several decades based on aging of the population

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

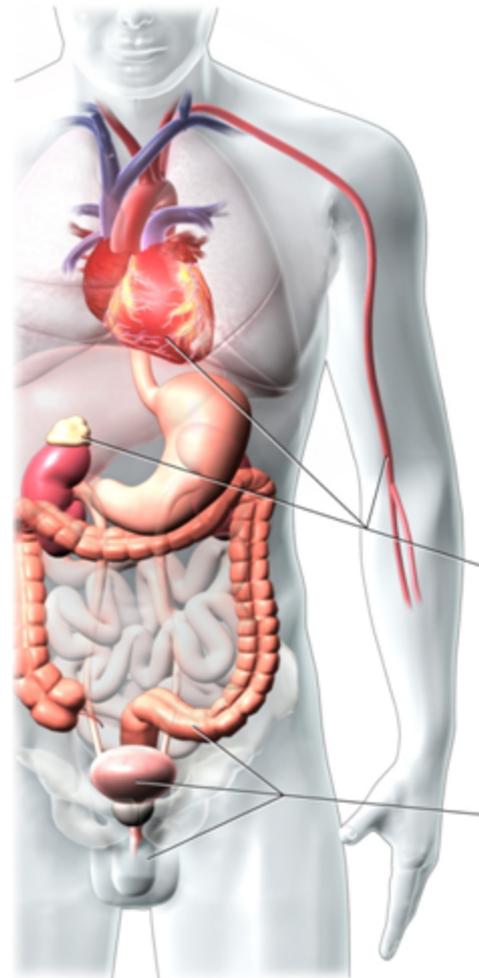


Sites of Neurodegeneration and Lewy Pathology in PD

- 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

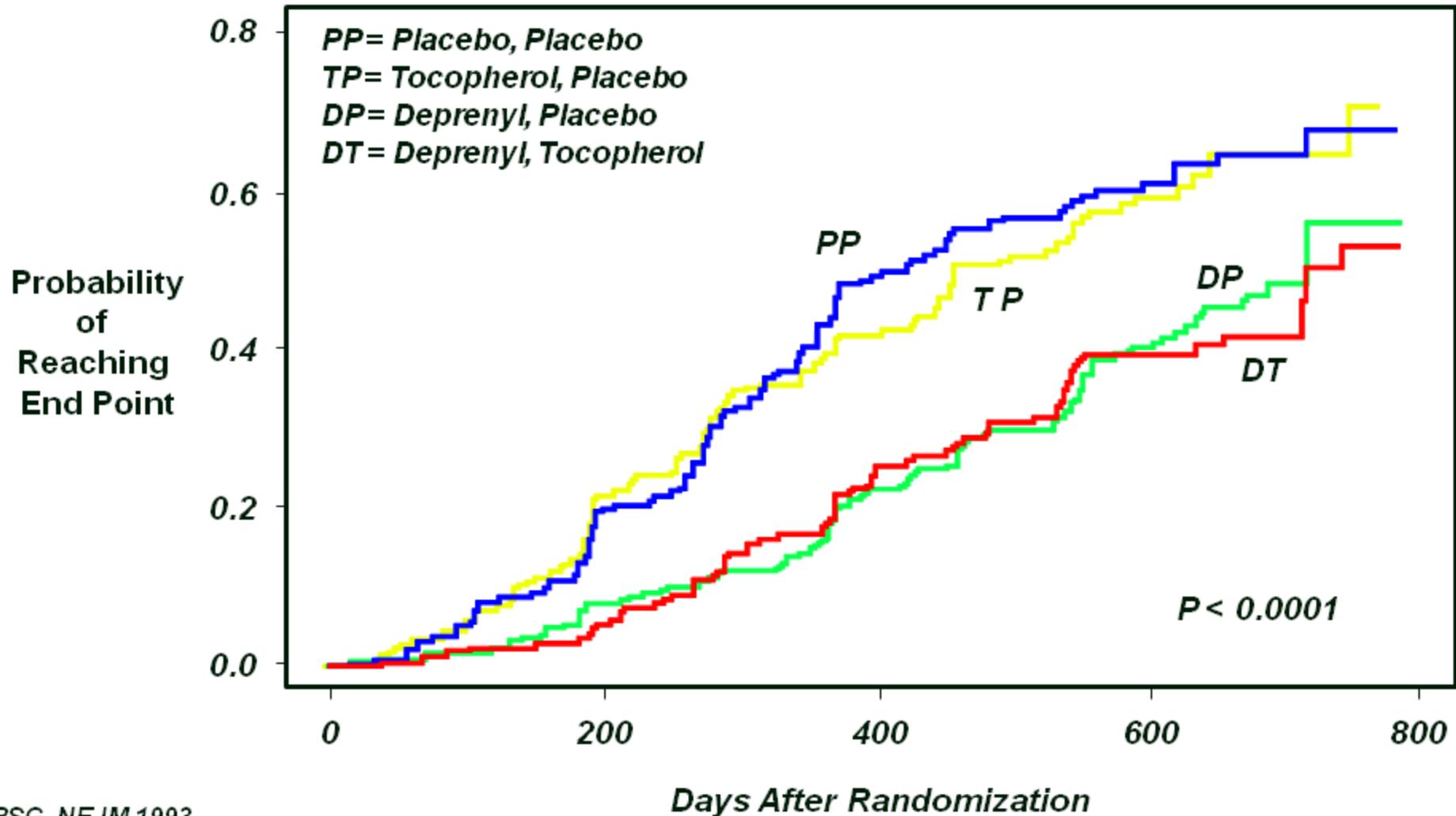
- A treatment intervention that slows, stops or reverses clinical progression, and prevents or limits the development of cumulative disability
 - Neuroprotection
 - Disease Modifying
 - Slowing Clinical Progression

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



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

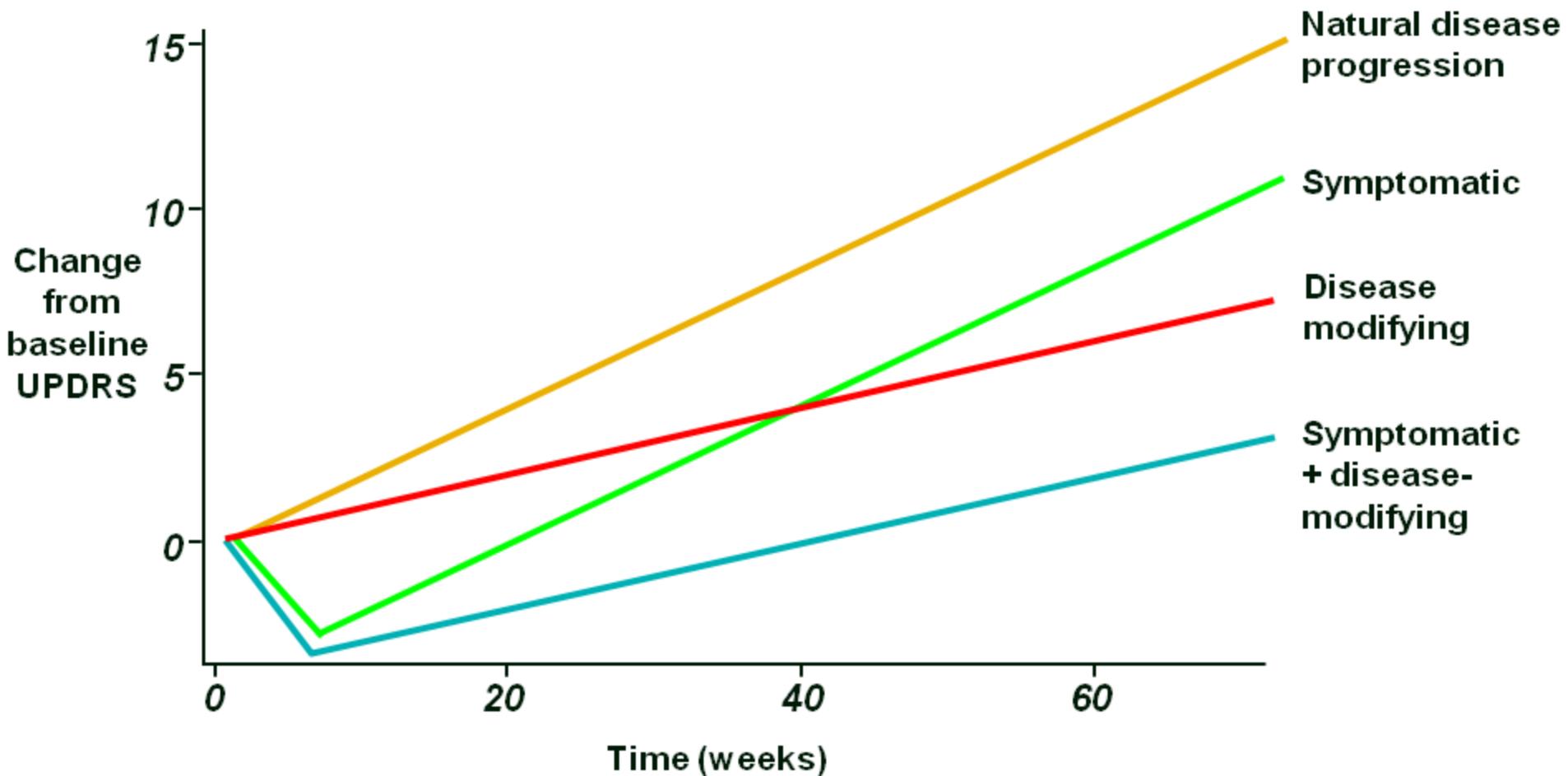
- Speech
- Salivation
- Swallowing
- Handwriting
- Cutting food
- Dressing
- Hygiene
- Turning in bed
- Falling
- Freezing
- Walking
- Tremor
- Sensory Complaints

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



Trial Designs to Assess Clinical Progression in PD

- Randomized Withdrawal
- Delayed Start Design

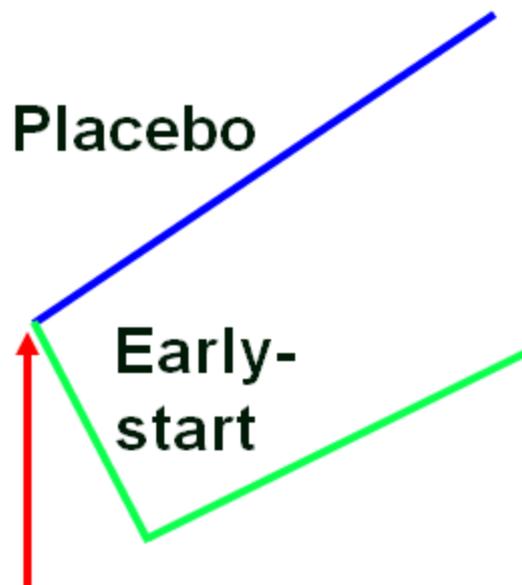
Delayed-start Design

Period I

Placebo

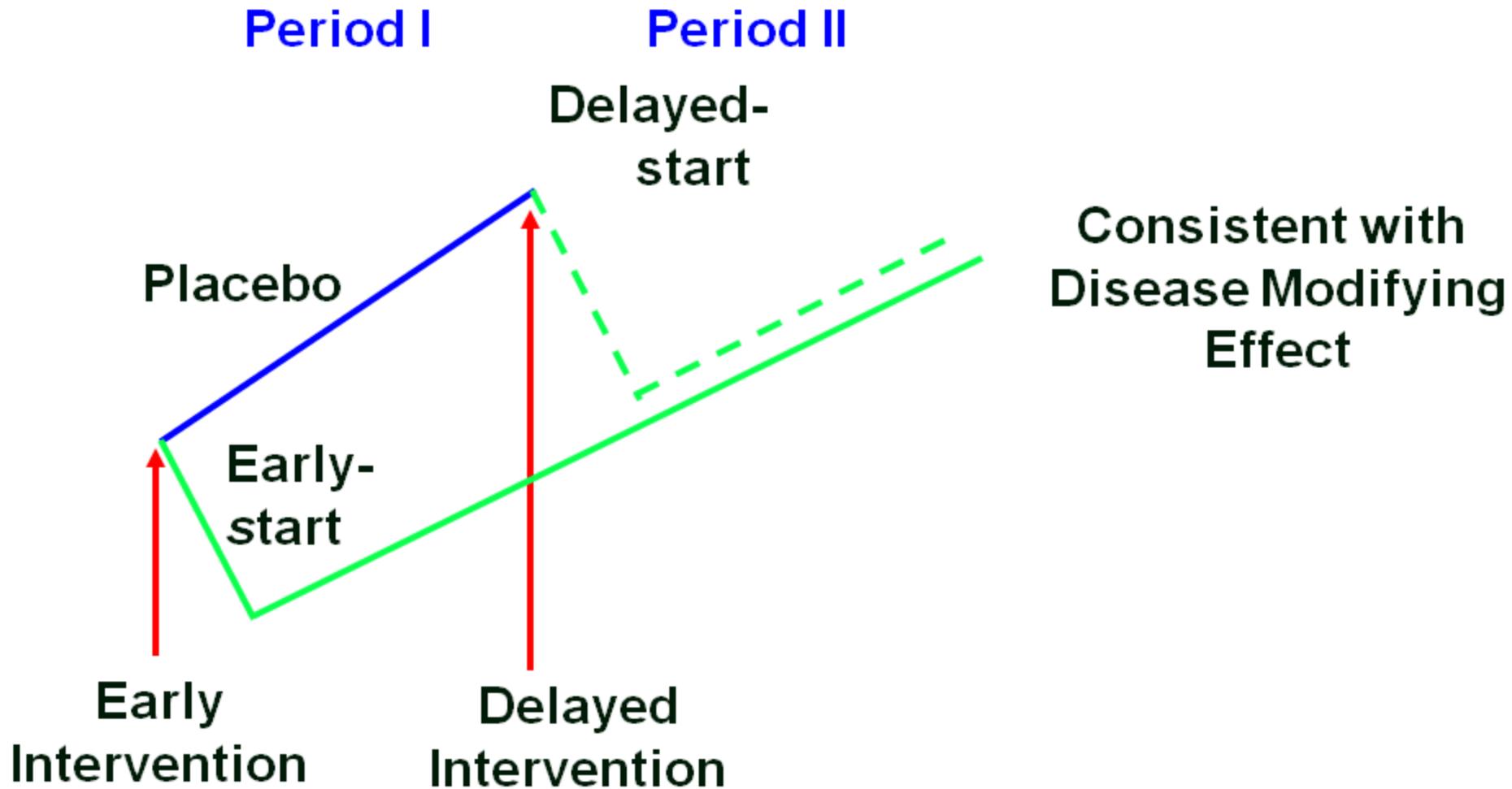
Early-
start

Early
Intervention

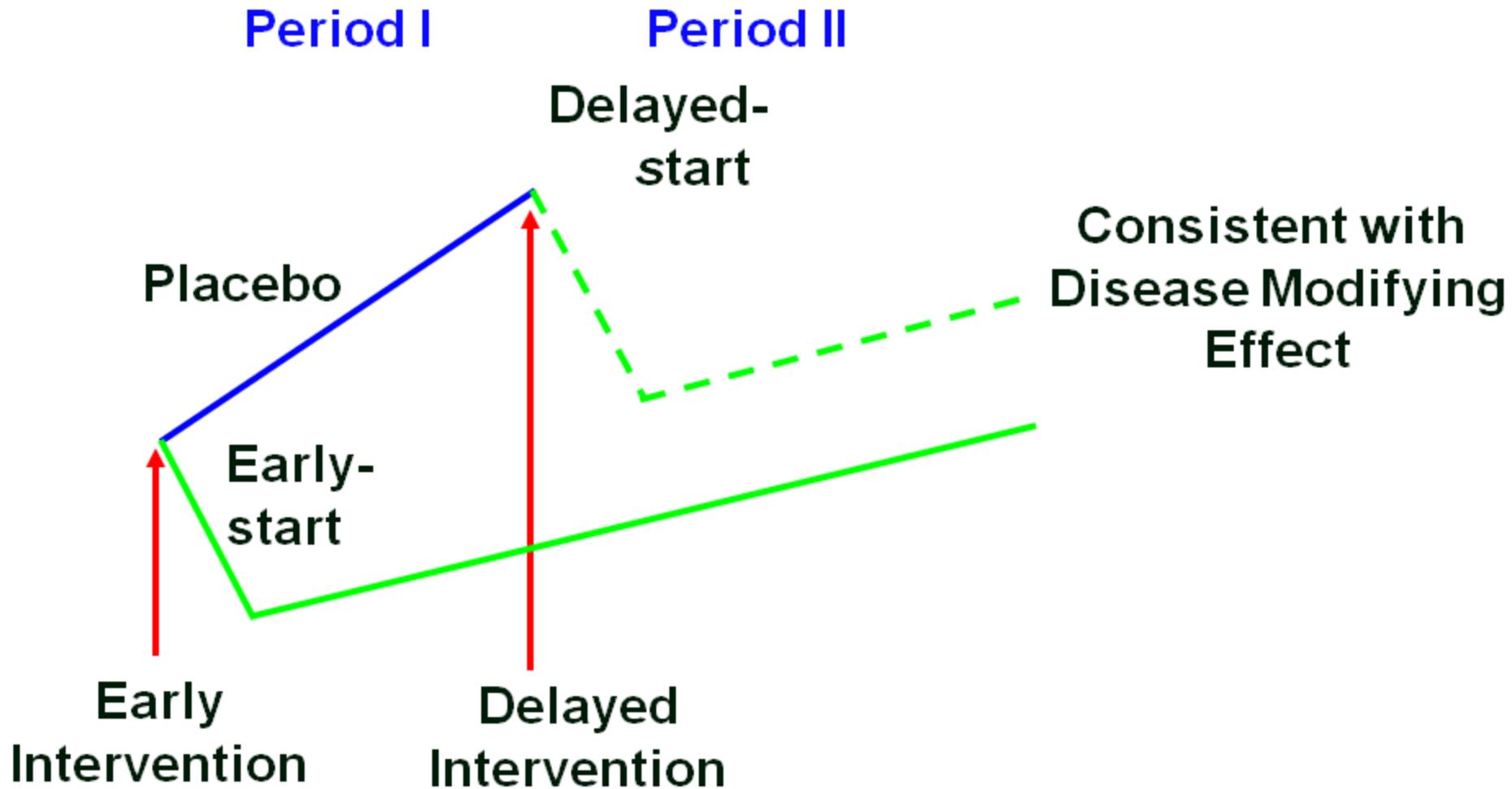


The diagram illustrates a delayed-start design. It features two lines representing the progression of two groups over time. The 'Placebo' group is represented by a blue line that starts at a certain point and rises linearly. The 'Early-start' group is represented by a green line that starts at a lower point, then rises linearly. A red arrow points upwards from the text 'Early Intervention' to the start of the green line, indicating the point at which the early intervention begins. The label 'Period I' is positioned above the lines, suggesting the time interval shown.

Delayed-start Design Symptomatic Effect



Delayed-start Design Slowing Clinical Progression



Delayed-start Design Study Issues

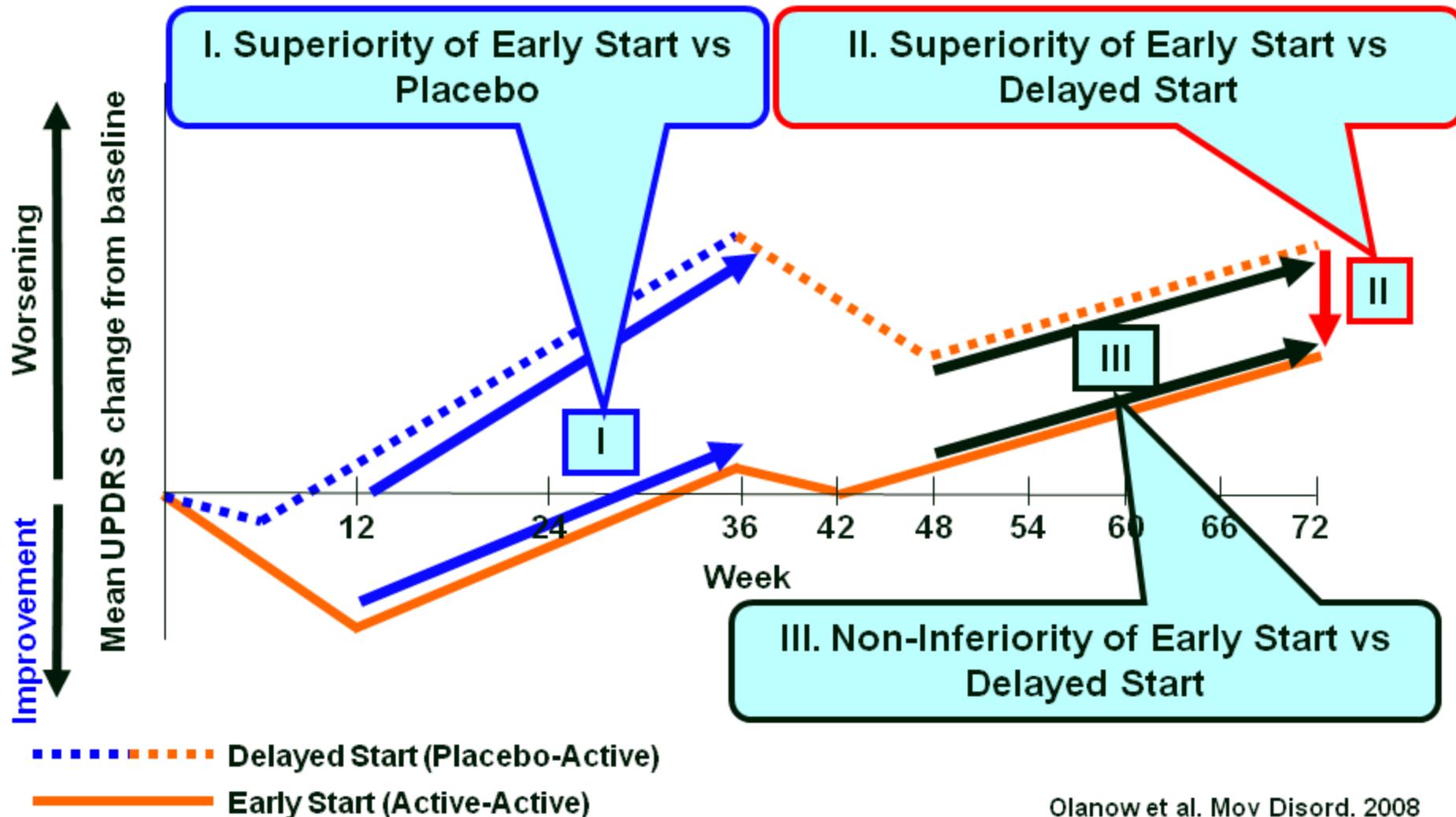
- Period I – must be long enough to show slowing of clinical progression
- Period II – must be long enough for full symptomatic effect to occur
- Periods I and II – must not be so long that patients withdraw because they need additional therapy
- Must be sufficient numbers of visits in periods I and 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



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.

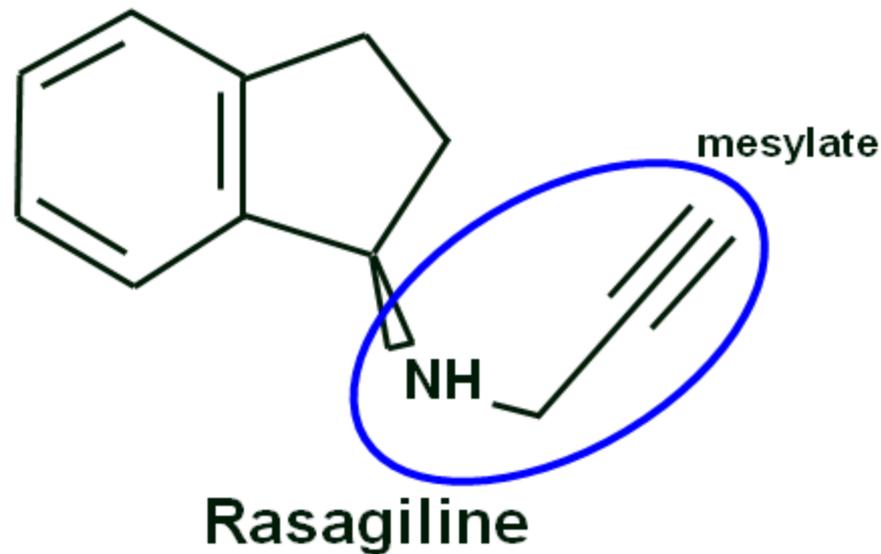
Director of Scientific and Medical Affairs

Teva Pharmaceuticals

Rasagiline Mesylate

N-propargyl-1(R)-aminoindan Mesylate

- MAO-B Inhibitor that incorporates a propargylamine structure



Rasagiline is Protective in Laboratory Models: In Vitro Models

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

Rasagiline is Protective in Laboratory Models: Animal Models

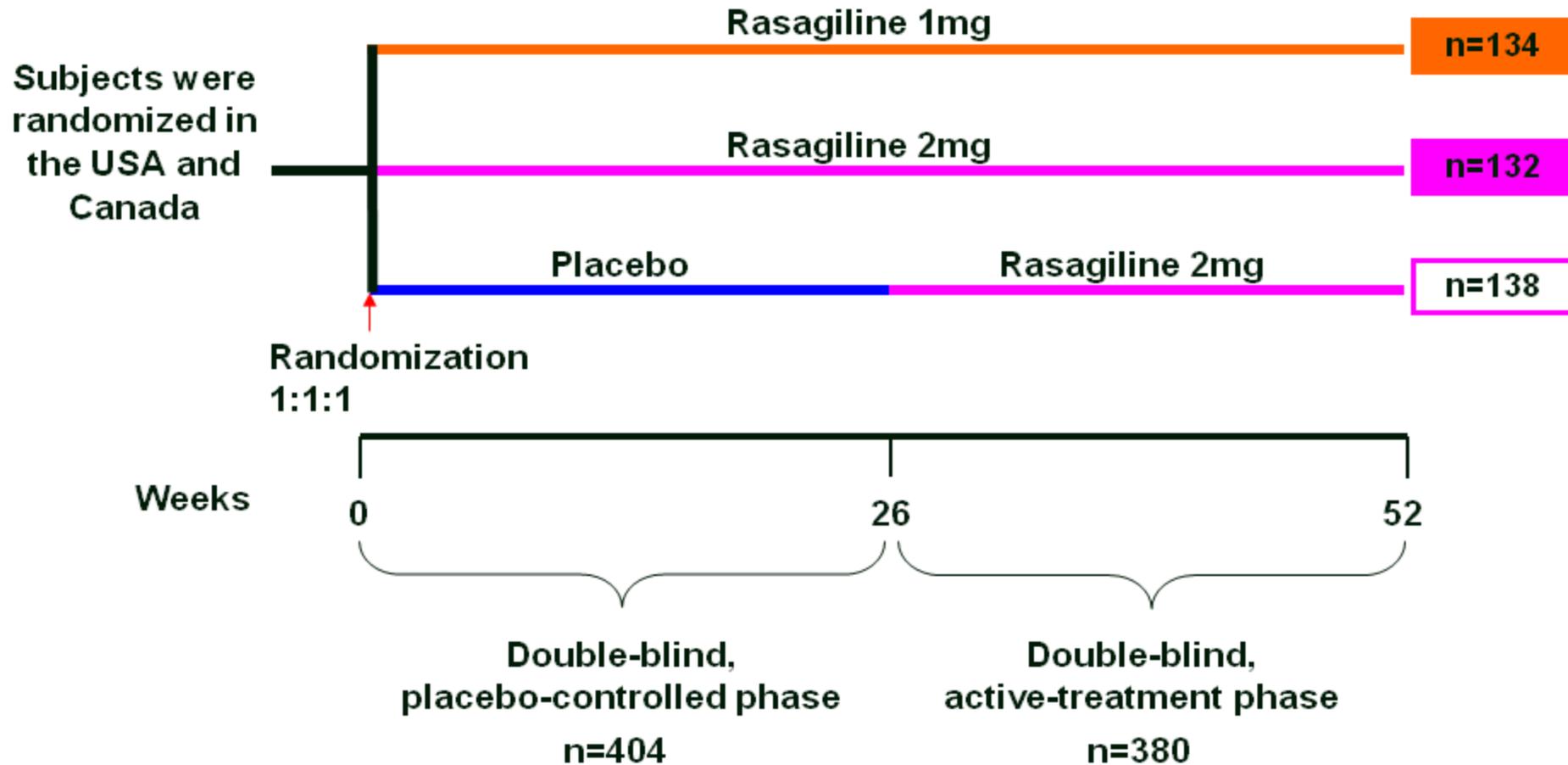
Model	Insult	Cytotoxic mechanism
Monkey	MPTP	Oxidative stress
Rat	Ischemia	Oxidative stress
Rat	SHP	Aging
Rat	Thiamine deficiency	Oxidative stress
Rat	6-OHDA	Oxidative stress
Mouse	MPTP	Neurotoxin
Mouse	Lactacystin	UPS inhibition
Mouse	3-NP (MSA model)	α-synuclein
Rat	6-OHDA and lactacystin	Oxidative stress and UPS inhibition

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

TEMPO Employed a Delayed-start Design



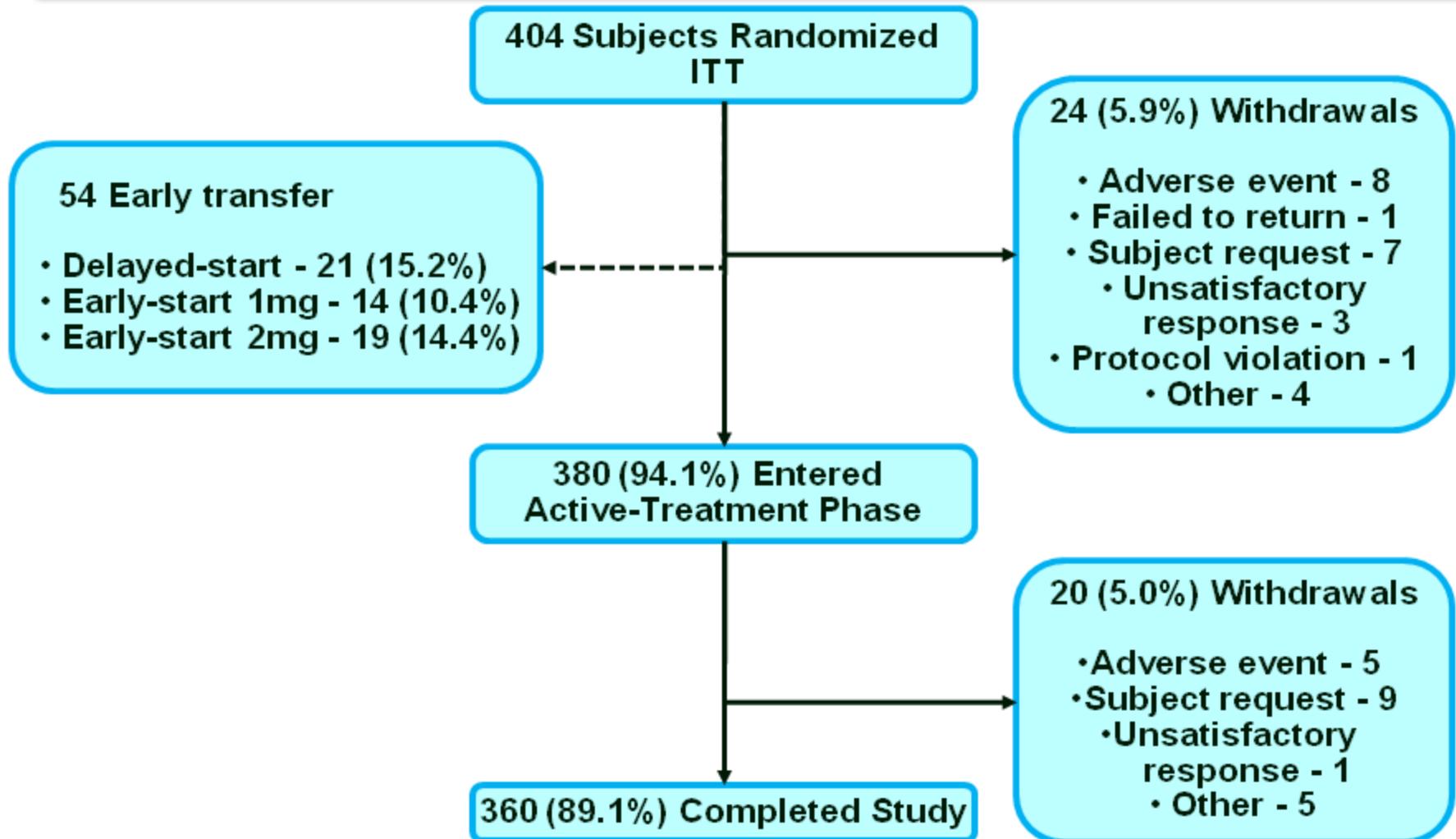
TEMPO: Designed to Recruit an Early and Mild PD Population

- 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



TEMPO: Similar Baseline Characteristics Across Groups

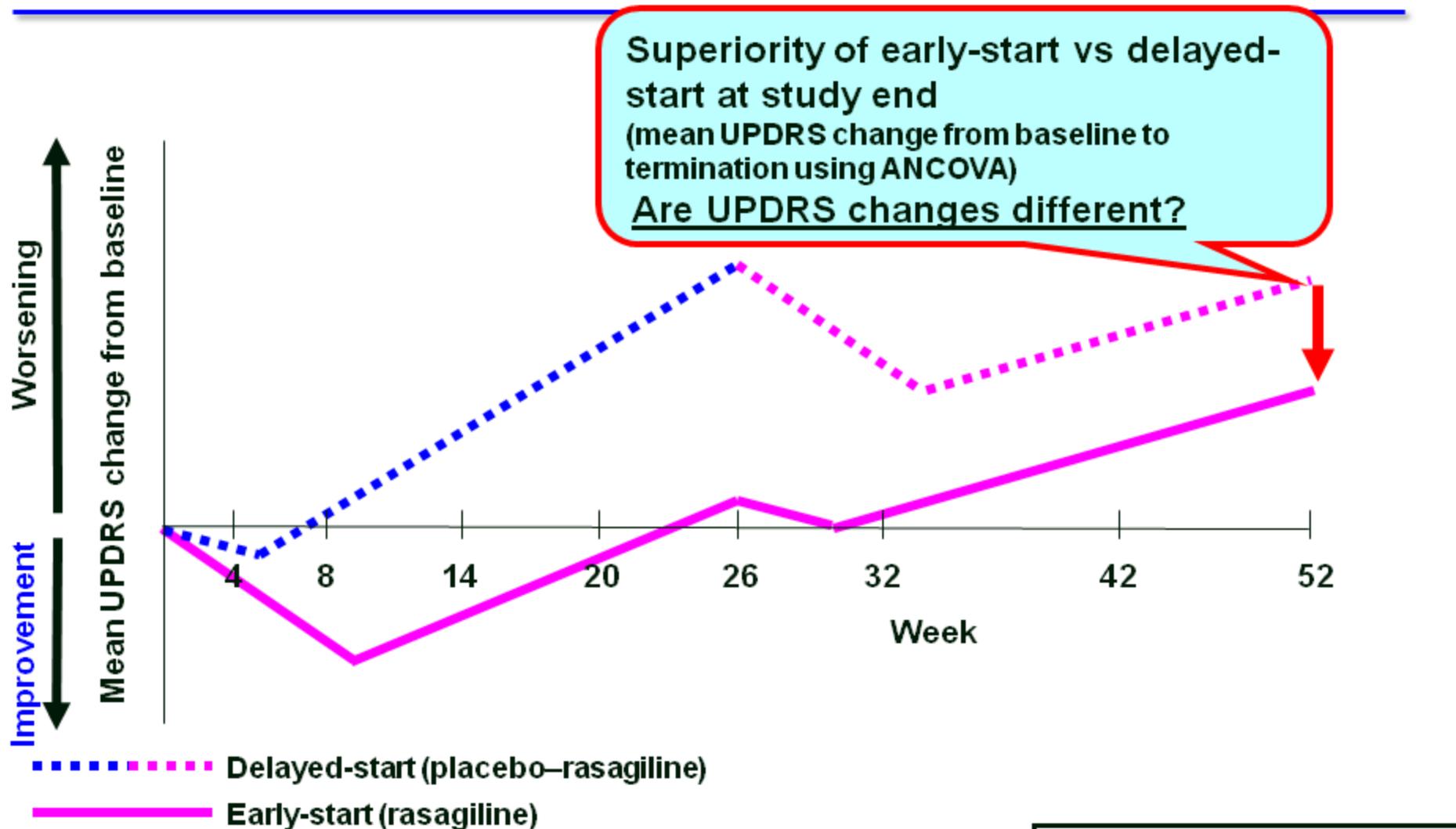
	Rasagiline 1mg early- start	Rasagiline 2mg early- start	Rasagiline 2mg delayed- start	All
Patients randomized (n)	134	132	138	404
Age, years (mean, SD)	61.6 (10.3)	60.4 (11.4)	60.5 (10.8)	60.8 (10.8)
Male patients (n, %)	90 (67.2)	74 (56.1)	93 (67.4)	257 (63.6)
PD duration, years (mean, SD)	11.1 (14.9)	13.9 (15.8)	11.3 (13.2)	12.1 (14.7)
UPDRS – Total score (mean, SD)	24.7 (11.3)	25.9 (9.5)	24.5 (11.6)	25.0 (10.8)
Hoehn & Yahr (mean, SD)	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)

TEMPO Efficacy Cohort Included 91.8% of Active-Treatment Phase

TEMPO	Rasagiline 1mg early- start	Rasagiline 2mg early- start	Rasagiline 2mg delayed- start	All
Randomized	134	132	138	404
Entered active-treatment phase	124	124	132	380
Efficacy Analysis of active-treatment phase*	122	119	130	371

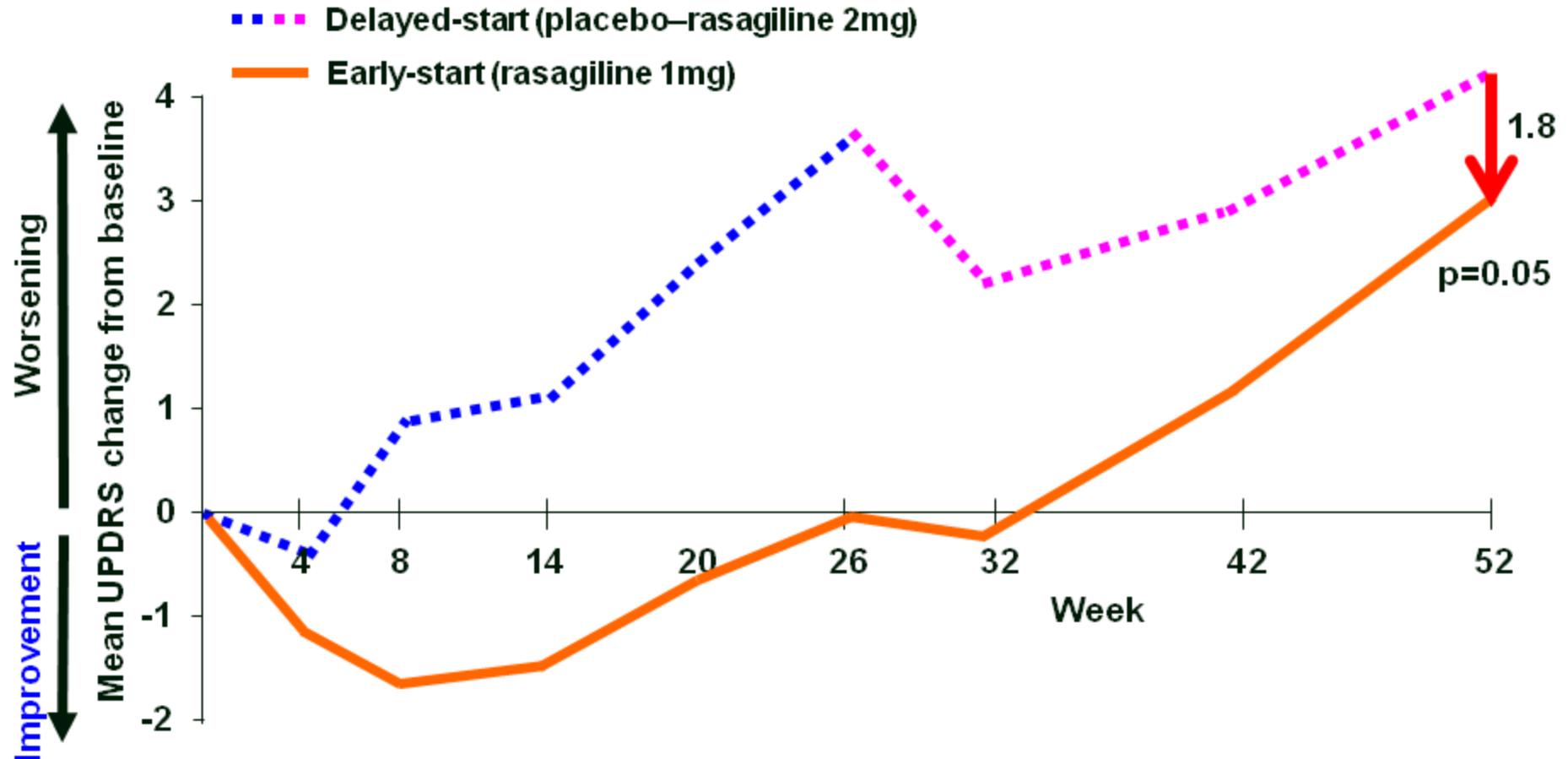
*at least 1 UPDRS measurement in the active phase without additional anti-PD therapy

TEMPO: 52 Week Analysis Used for Slowing of Clinical Progression Assessment

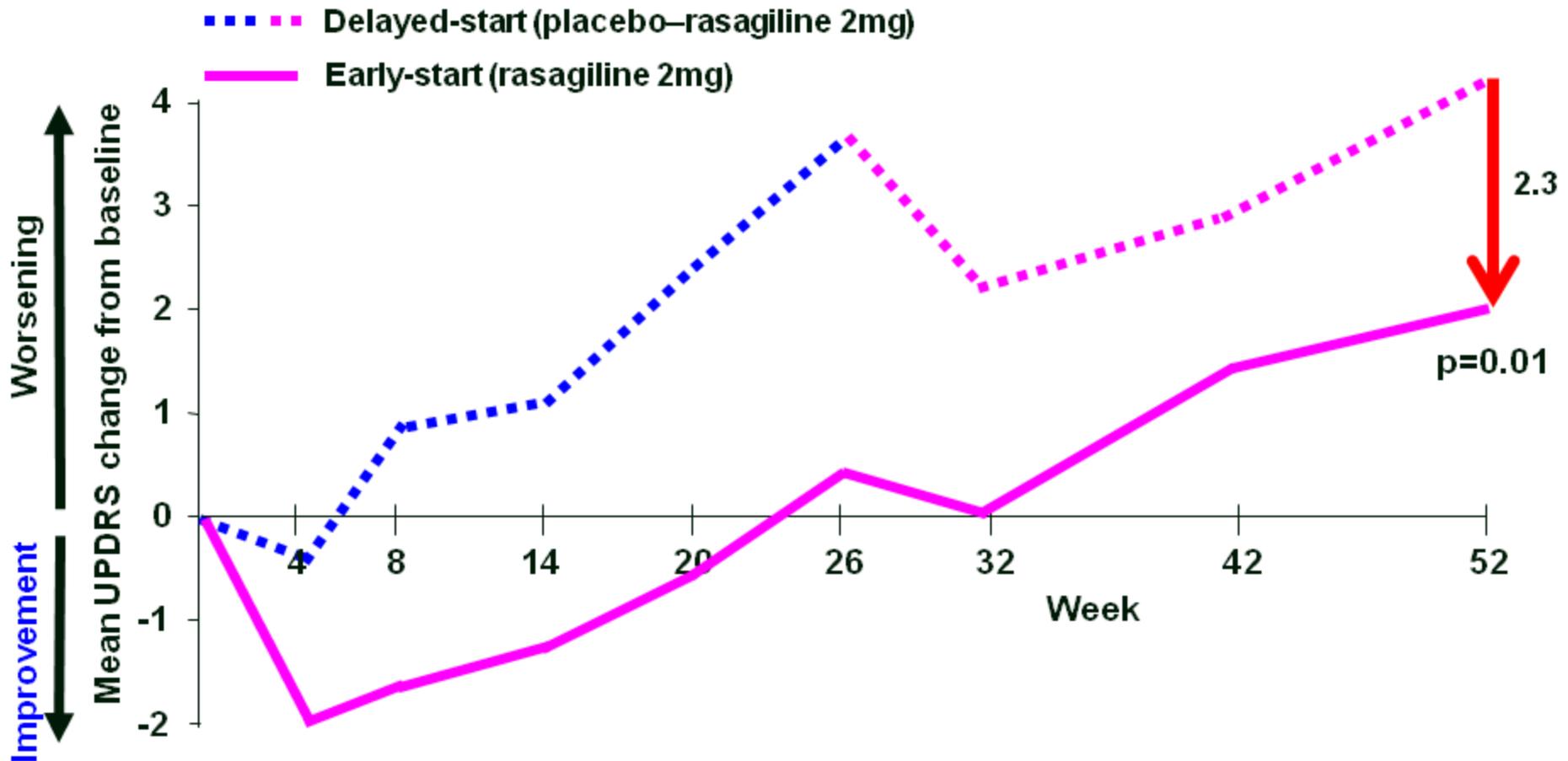


Schematic illustration

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



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



TEMPO: Differences Cannot be Fully Explained by Rasagiline's Symptomatic Effects

ORIGINAL CONTRIBUTION

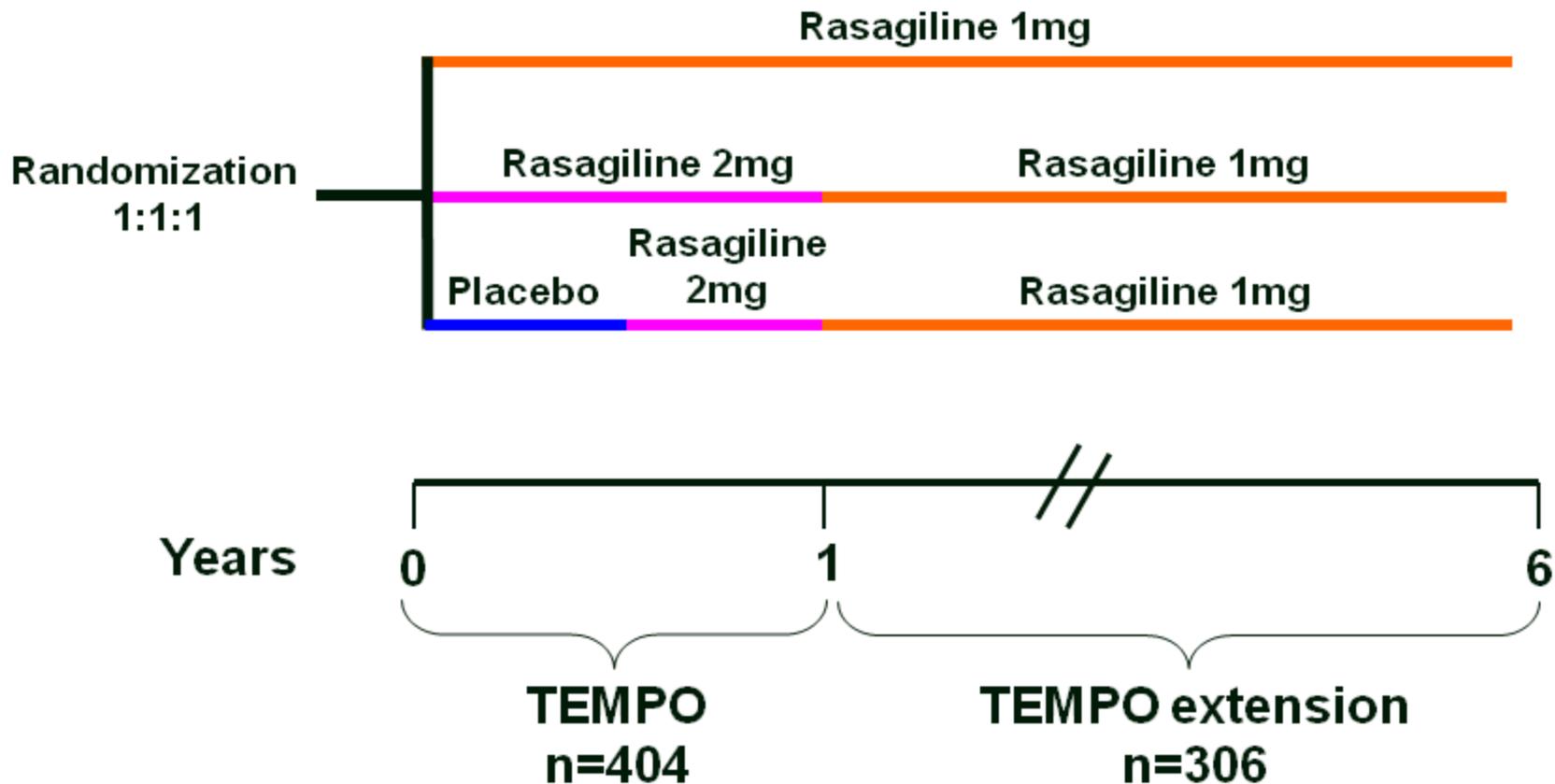
A Controlled, Randomized, Delayed-Start Study of Rasagiline in Early Parkinson Disease

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.”

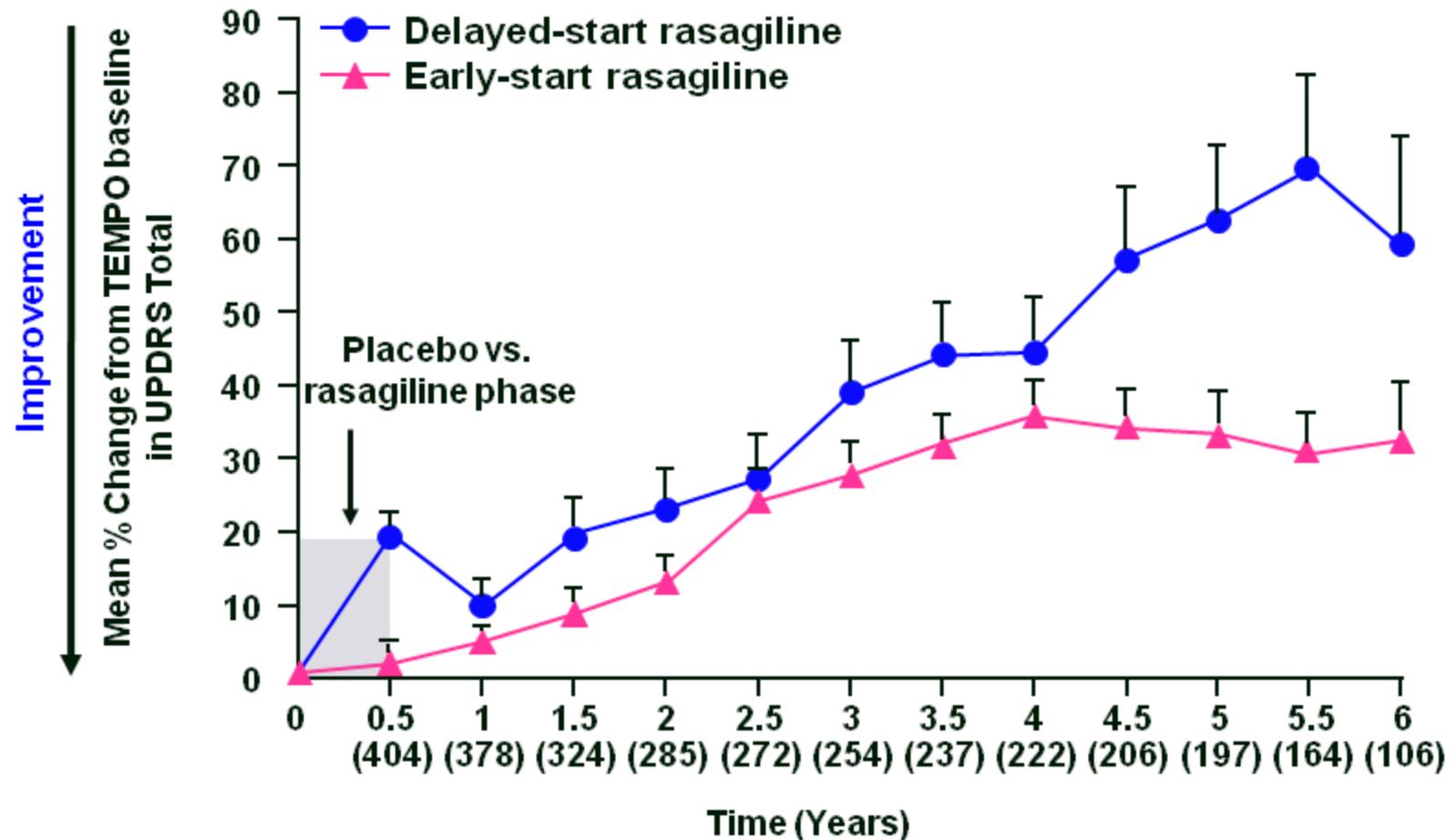
TEMPO Long-term: Patients Took Rasagiline 1mg & Additional Parkinsonian Medication



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%, $p=0.006$

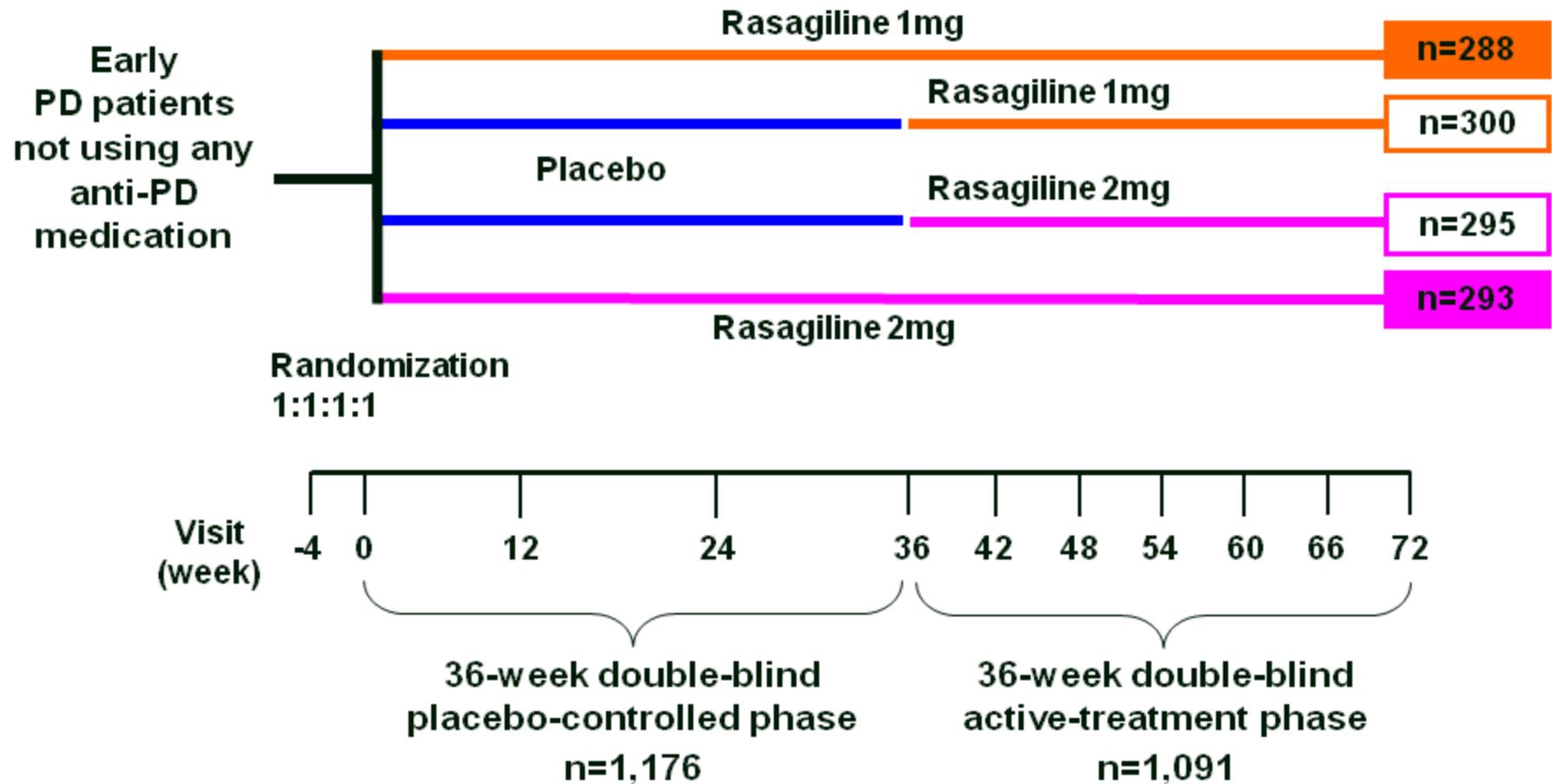


ADAGIO Study Objective

Attenuation of Disease Progression with Azilect Given Once-daily

- Main Objective: Investigate the effect of rasagiline on clinical progression of Parkinson's disease

ADAGIO: Designed to Assess Effects on Slowing of Clinical Progression



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

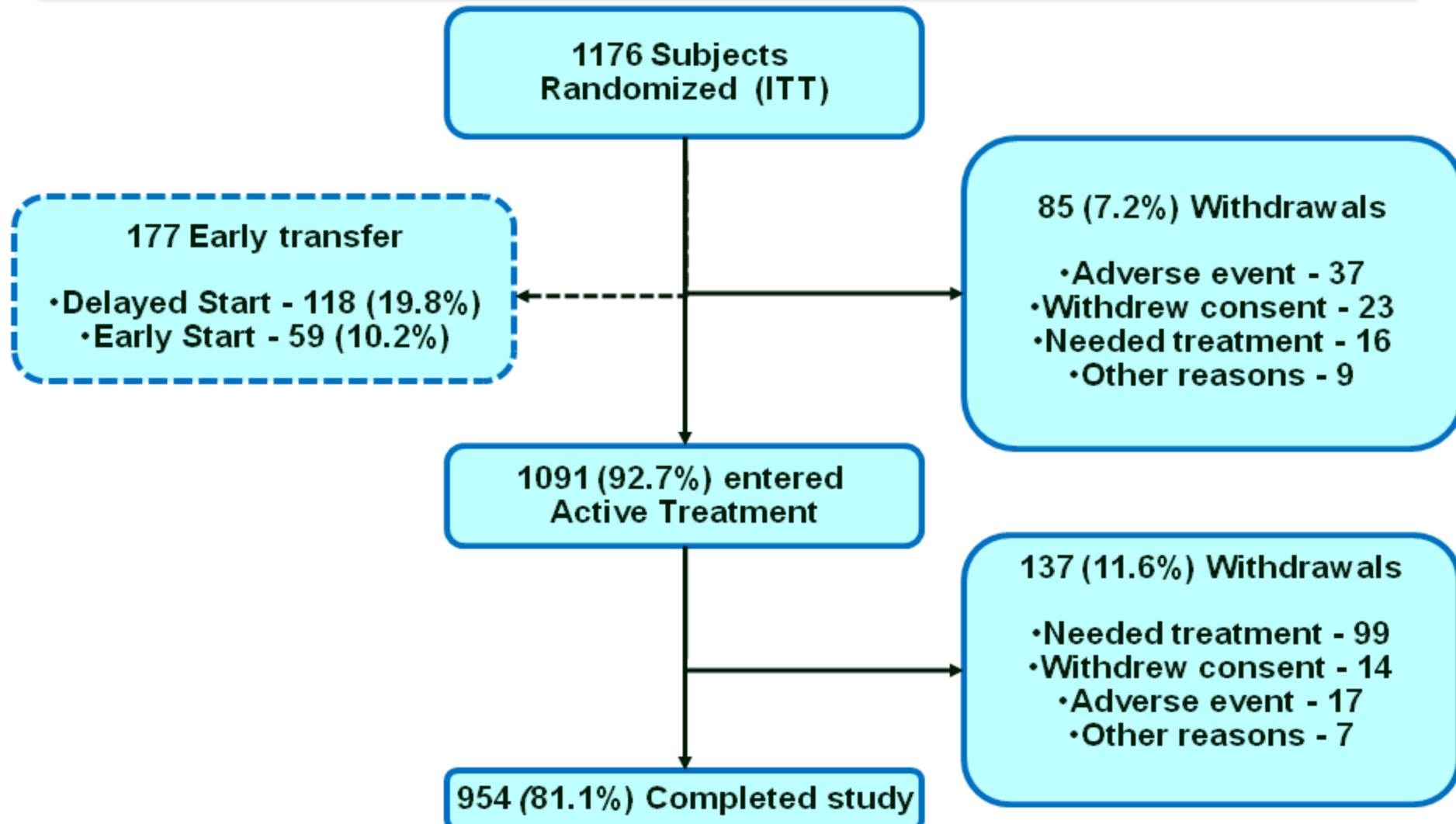
■ Exclusion criteria

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

ADAGIO: No Other Parkinsonian Therapy was Allowed

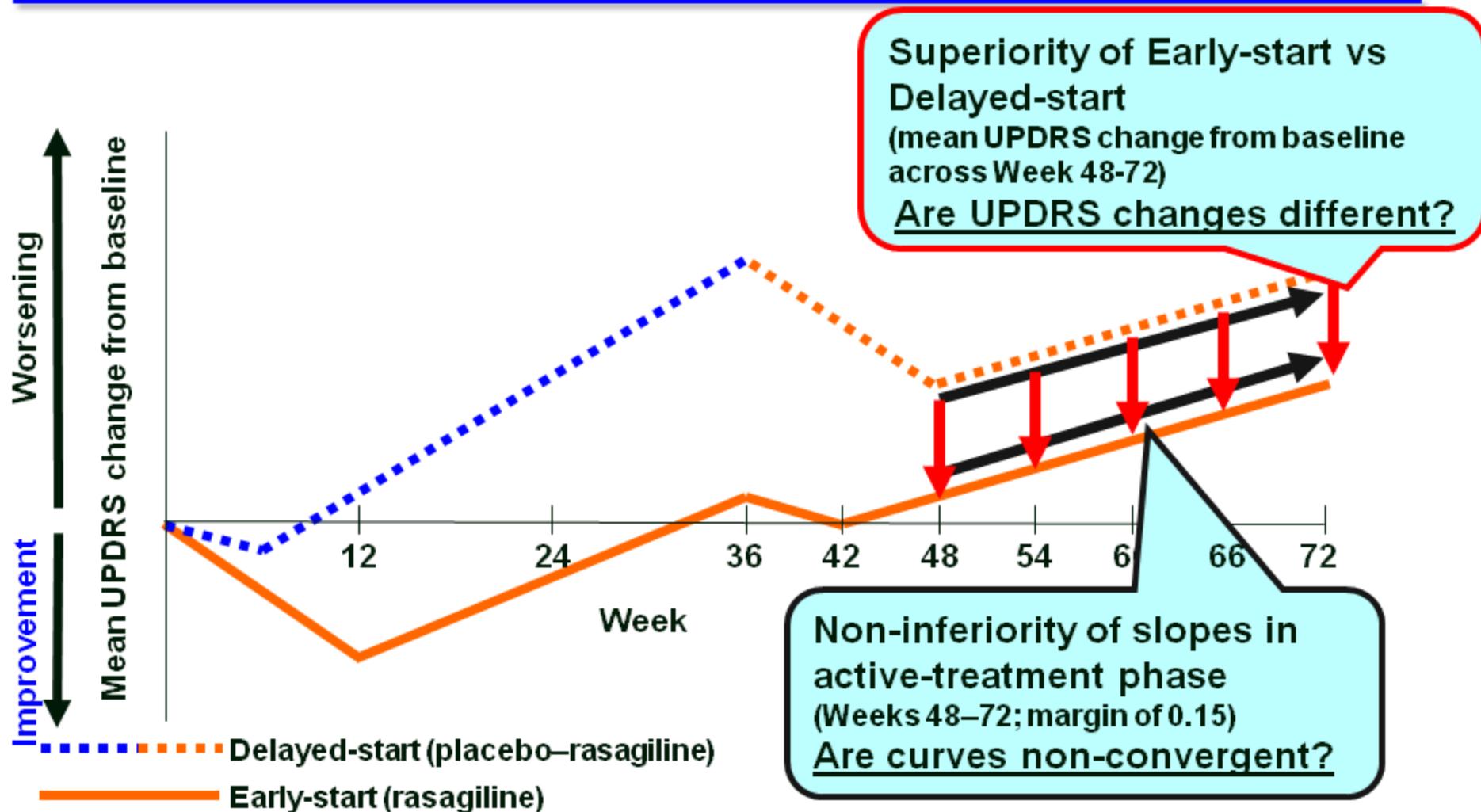
- Placebo-controlled phase
 - If investigator determined subject needed additional anti-PD therapy, subject proceeded to the active-treatment phase
- Active-treatment phase
 - If investigator determined subject needed additional anti-PD therapy, subject was prematurely withdrawn from the study

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



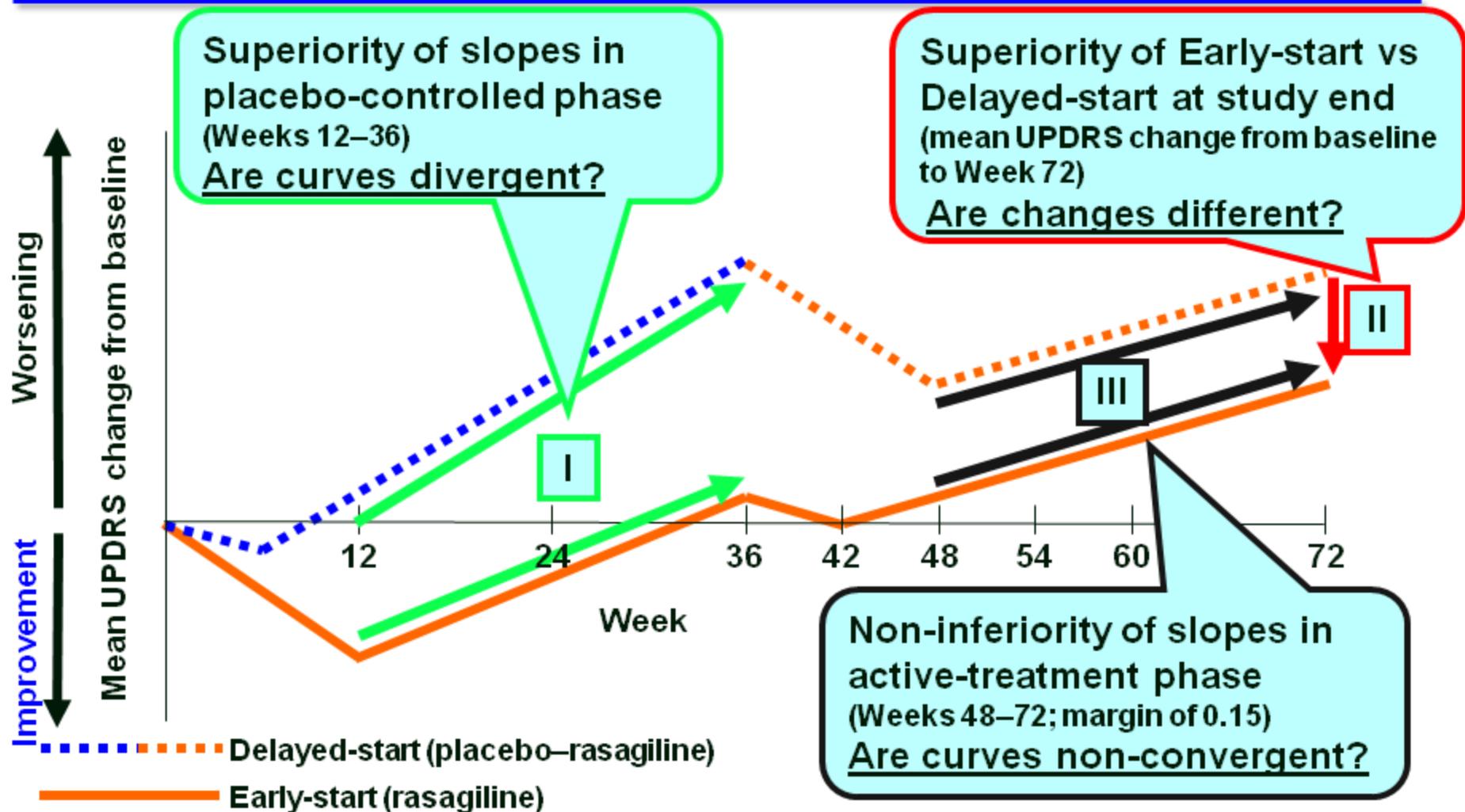
Evolution of ADAGIO Study Design and Analyses

ADAGIO: Original 2 Endpoints Required to Show Slowing of Clinical Progression



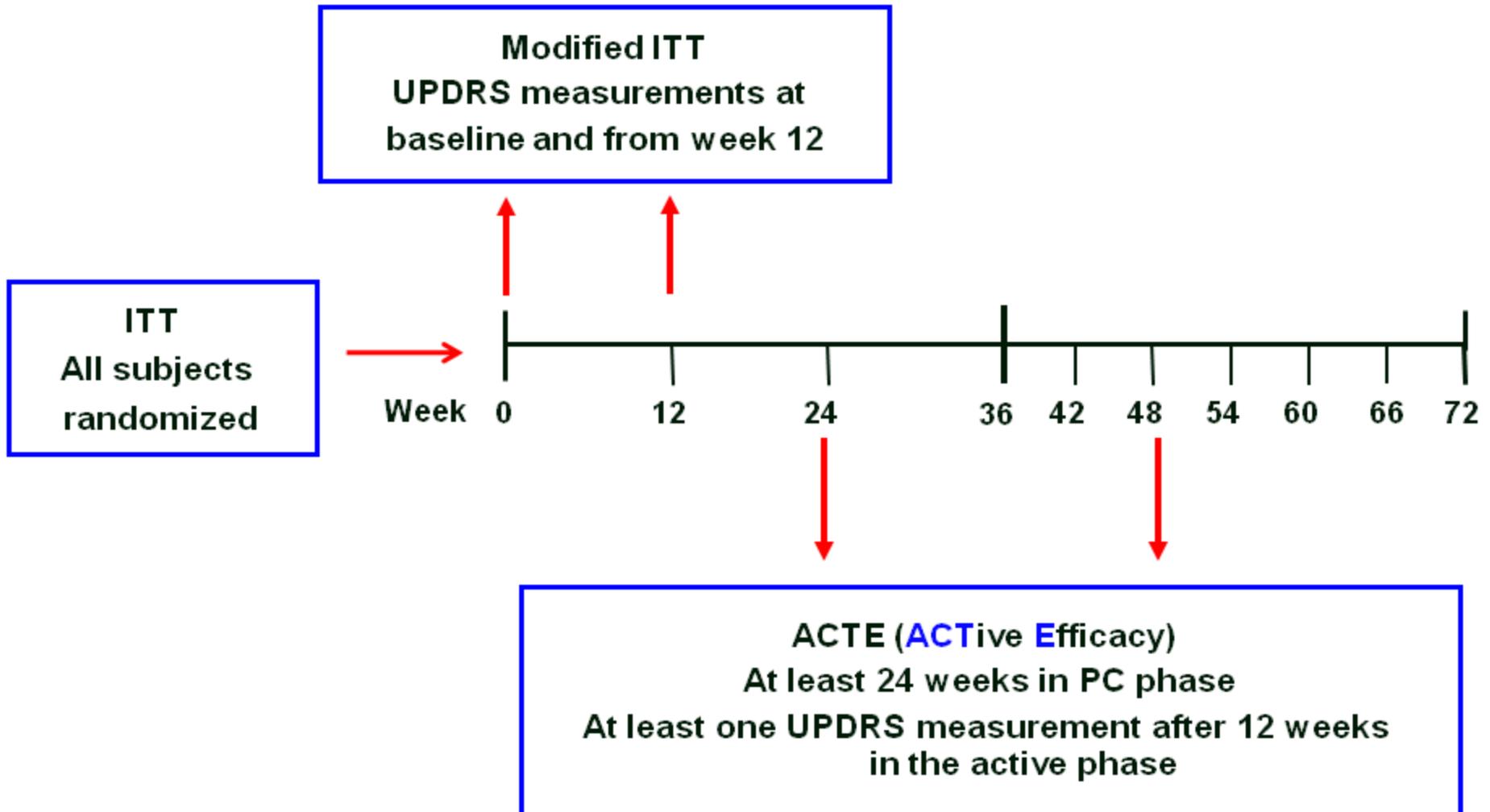
Schematic illustration

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

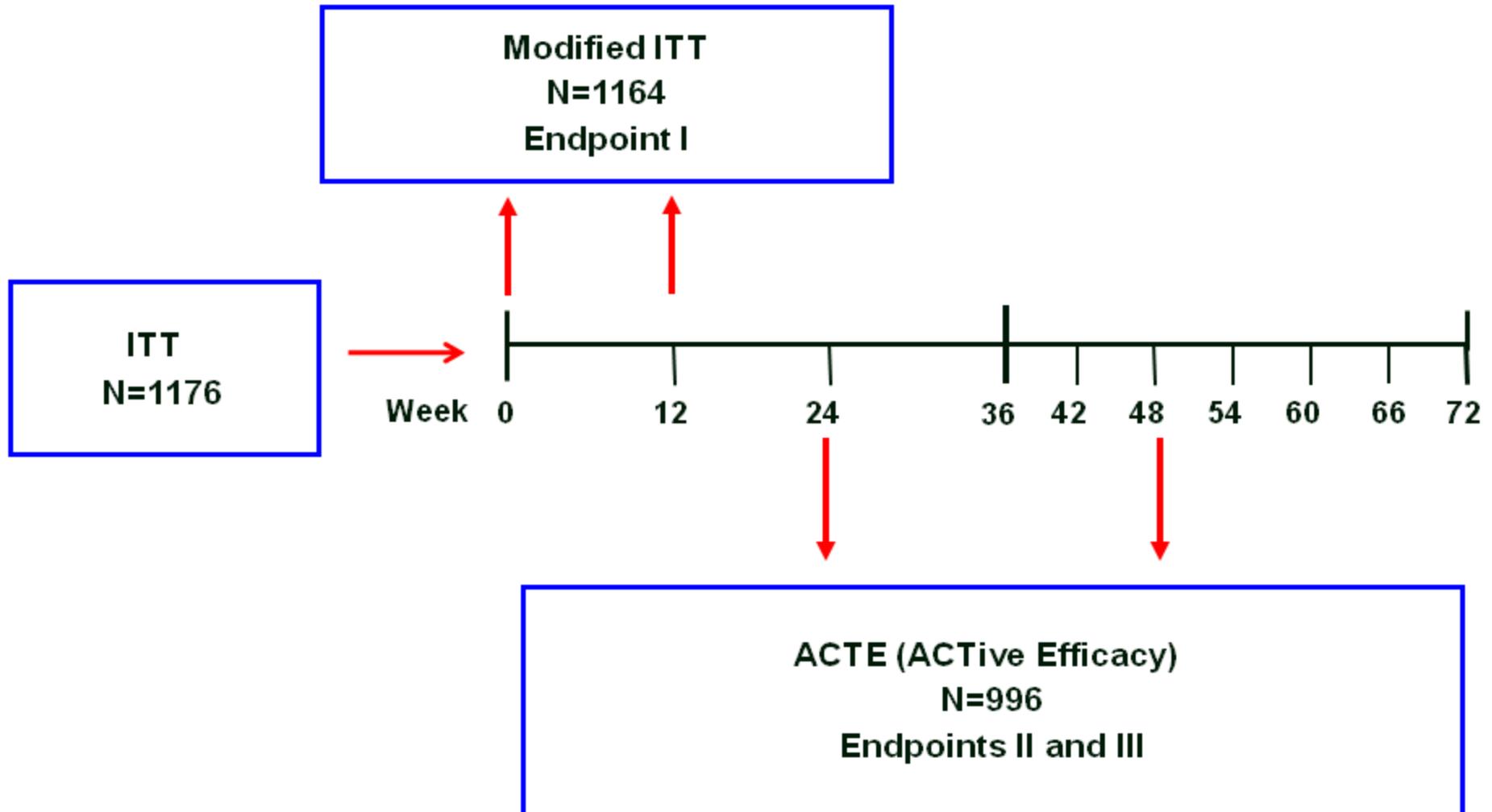


Schematic illustration

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



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



ADAGIO: Similar Baseline Characteristics Across Groups, All with Early and Mild PD

	Rasagiline 1mg delayed- start	Rasagiline 1mg early- start	Rasagiline 2mg delayed- start	Rasagiline 2mg early- start	All
Patients (n)	300	288	295	293	1,176
Age, yrs (mean, SD)	61.9 (9.7)	62.4 (9.7)	62.4 (9.7)	62.3 (9.6)	62.2 (9.7)
Male patients (n, %)	186 (62.0)	175 (60.8)	182 (61.7)	175 (59.7)	718 (61.1)
PD duration, months (mean, SD)	4.3 (4.6)	4.6 (4.7)	4.6 (4.6)	4.6 (4.6)	4.5 (4.6)
UPDRS total score (mean, SD)	20.2 (8.8)	20.6 (8.4)	19.9 (8.1)	20.8 (8.8)	20.4 (8.5)
Hoehn & Yahr (mean, SD)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)

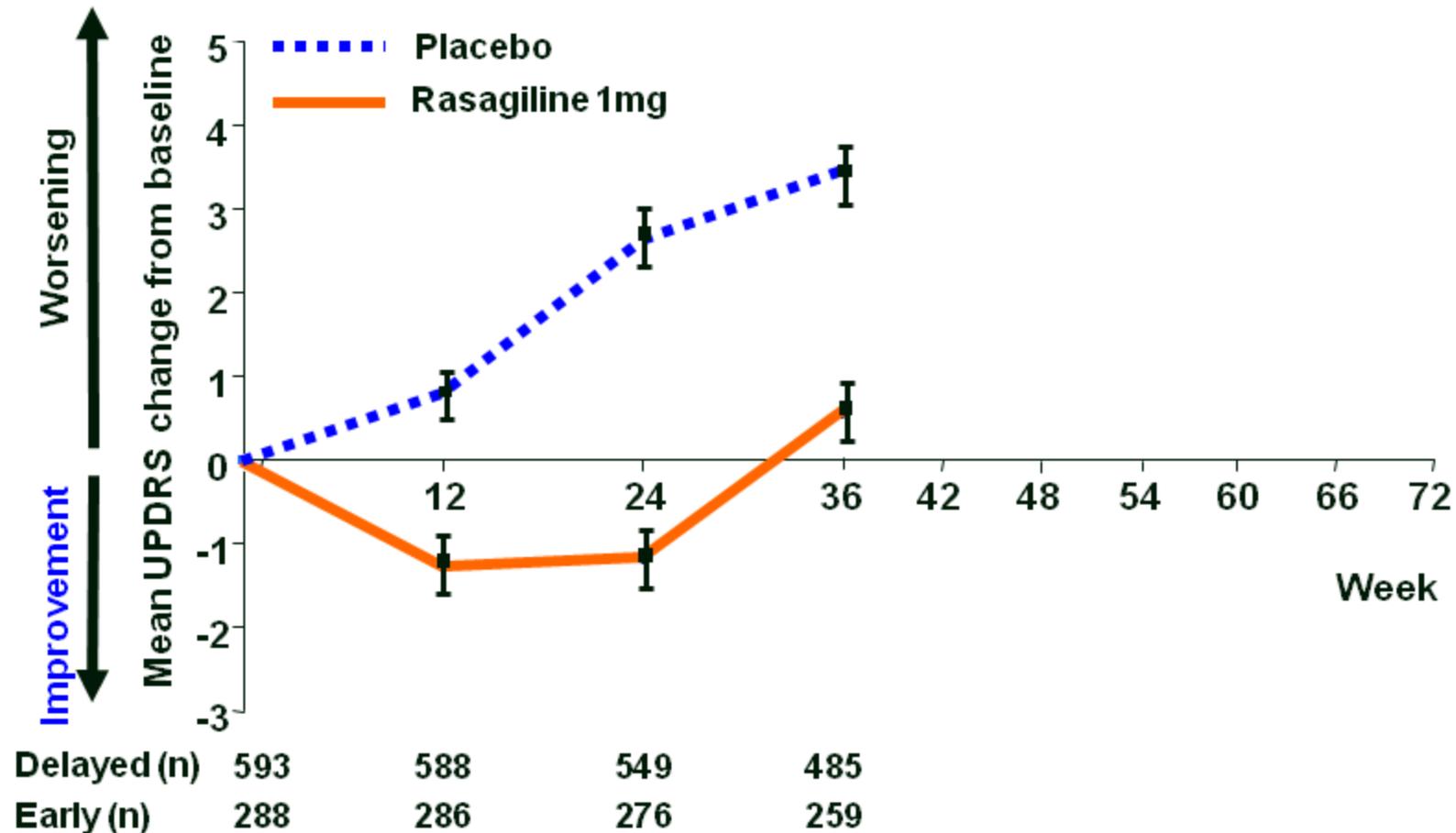
ADAGIO: Similar Baseline Characteristics Between ITT, Modified ITT, and ACTE Cohorts

	ITT	mITT	ACTE
Patients (n)	1176	1164	996
Male patients (n, %)	718 (61.1)	709 (60.9)	603 (60.5)
Age, years (mean, SD)	62.2 (9.6)	62.2 (9.6)	62.4 (9.4)
PD duration, months (mean, SD)	4.5 (4.6)	4.5 (4.6)	4.6 (4.6)
UPDRS total score (mean, SD)	20.4 (8.5)	20.4 (8.5)	19.8 (8.2)
Modified Hoehn & Yahr (mean, SD)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)

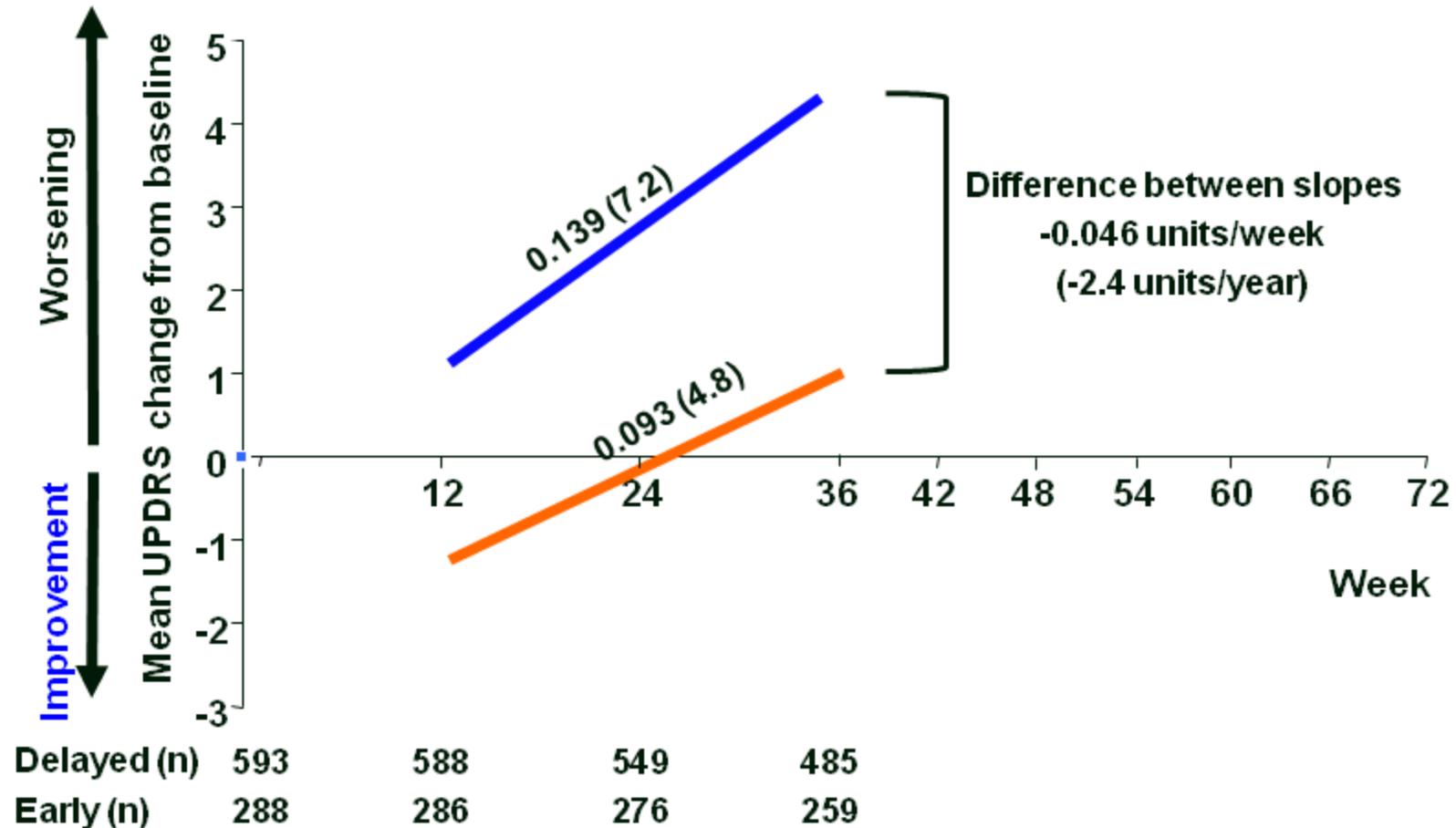
ADAGIO: ACTE Baseline Characteristics

	Rasagiline 1mg delayed- start	Rasagiline 1mg early- start	Rasagiline 2mg delayed- start	Rasagiline 2mg early- start	All
Patients (n)	238	251	249	258	996
Age, yrs (mean, SD)	62.2 (9.2)	62.9 (9.5)	62.5 (9.3)	62.2 (9.8)	62.4 (9.4)
Male patients (n, %)	147 (61.8)	153 (61.0)	152 (61.0)	151 (58.5)	603 (60.5)
PD duration, months (mean, SD)	4.5 (4.7)	4.8 (4.8)	4.5 (4.5)	4.5 (4.4)	4.6 (4.6)
UPDRS total score (mean, SD)	19.10 (8.07)	20.53 (8.45)	19.24 (7.87)	20.27 (8.45)	19.80 (8.23)
Hoehn & Yahr (mean, SD)	1.50 (0.49)	1.52 (0.49)	1.44 (0.47)	1.50 (0.49)	1.49 (0.48)

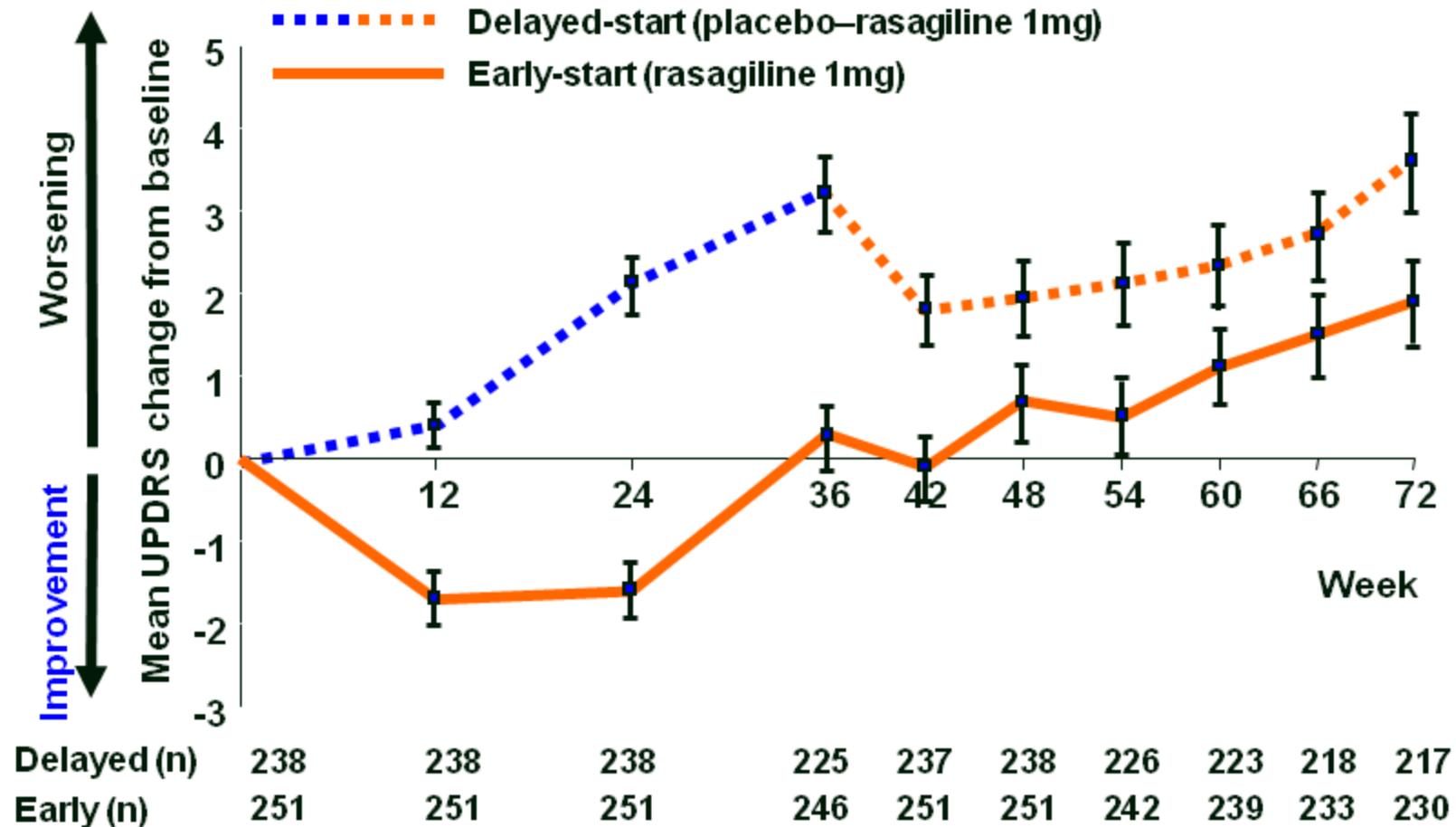
ADAGIO: Rasagiline 1mg Observed Data for Modified ITT Cohort (Weeks 0-36)



ADAGIO: Rasagiline 1mg Observed Data for Modified ITT Cohort (Weeks 0-36)



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

The ADAGIO Study Publication

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

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

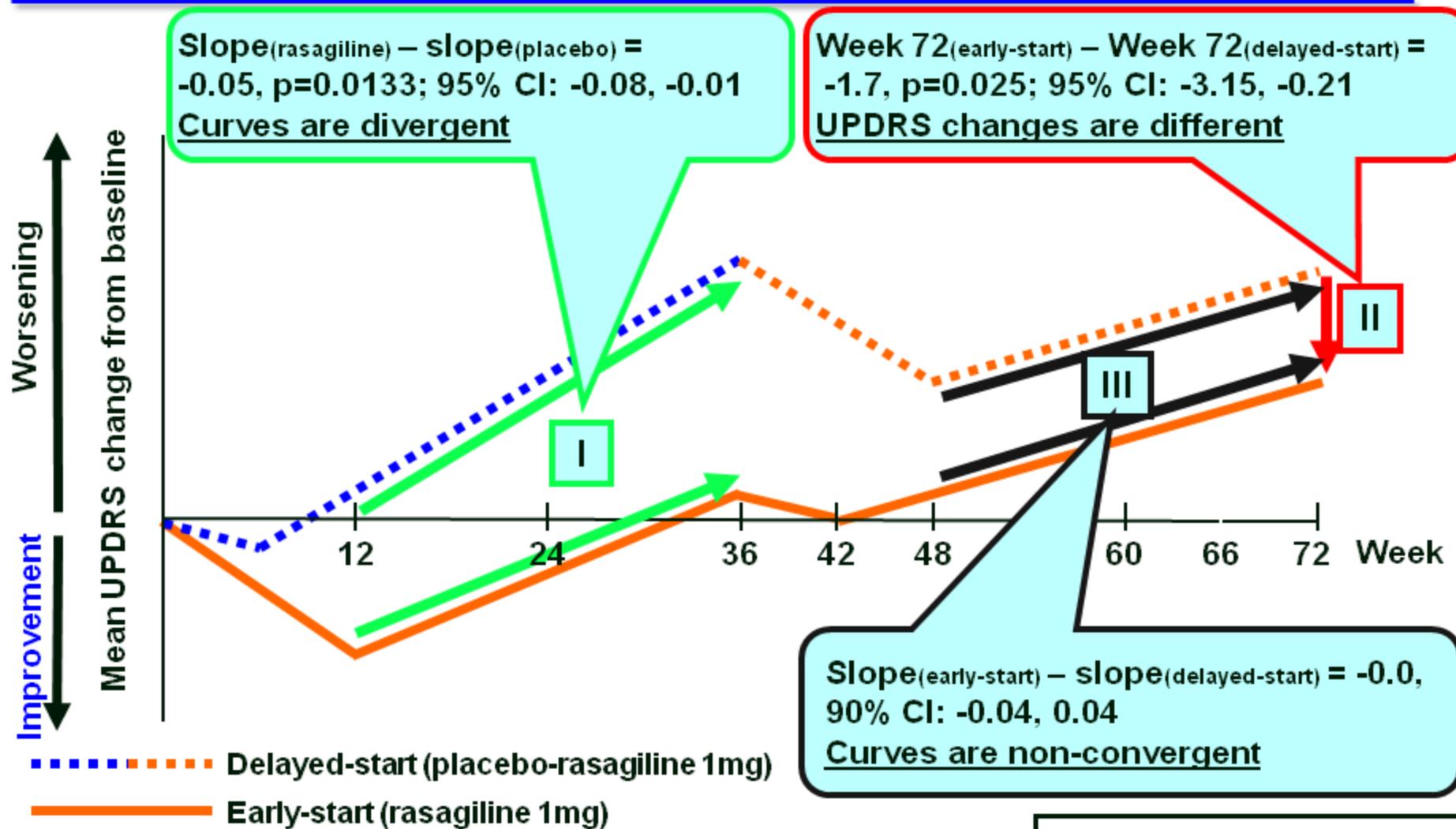
	<u>Final SAP</u> Week 72 only combined data set	<u>Alternative</u> Week 72 only separate data sets	<u>Original SAP</u> Weeks 48-72 combined data set
Early-Start <small>(Week 72) -</small> Delayed-start <small>(Week 72)</small>	-1.4	-1.7	-1.4
(UPDRS units)			
P-value	0.051	0.025	0.012

ADAGIO Results: 1mg Dose Endpoint III

	<u>Final SAP</u> Week 72 only Combined Data Set	<u>Alternative</u> Week 72 only Separate Data Sets
Slope <small>(Delayed-Start)</small> - Slope <small>(Early-Start)</small> (UPDRS-Total Units/Week)	0.0	0.0
Upper Limit of 90% CI	0.027	0.036

Required Criteria for Upper Limit of 90% CI = 0.15

ADAGIO Alternative Analysis: Results Support Disease Modifying Effect of Rasagiline

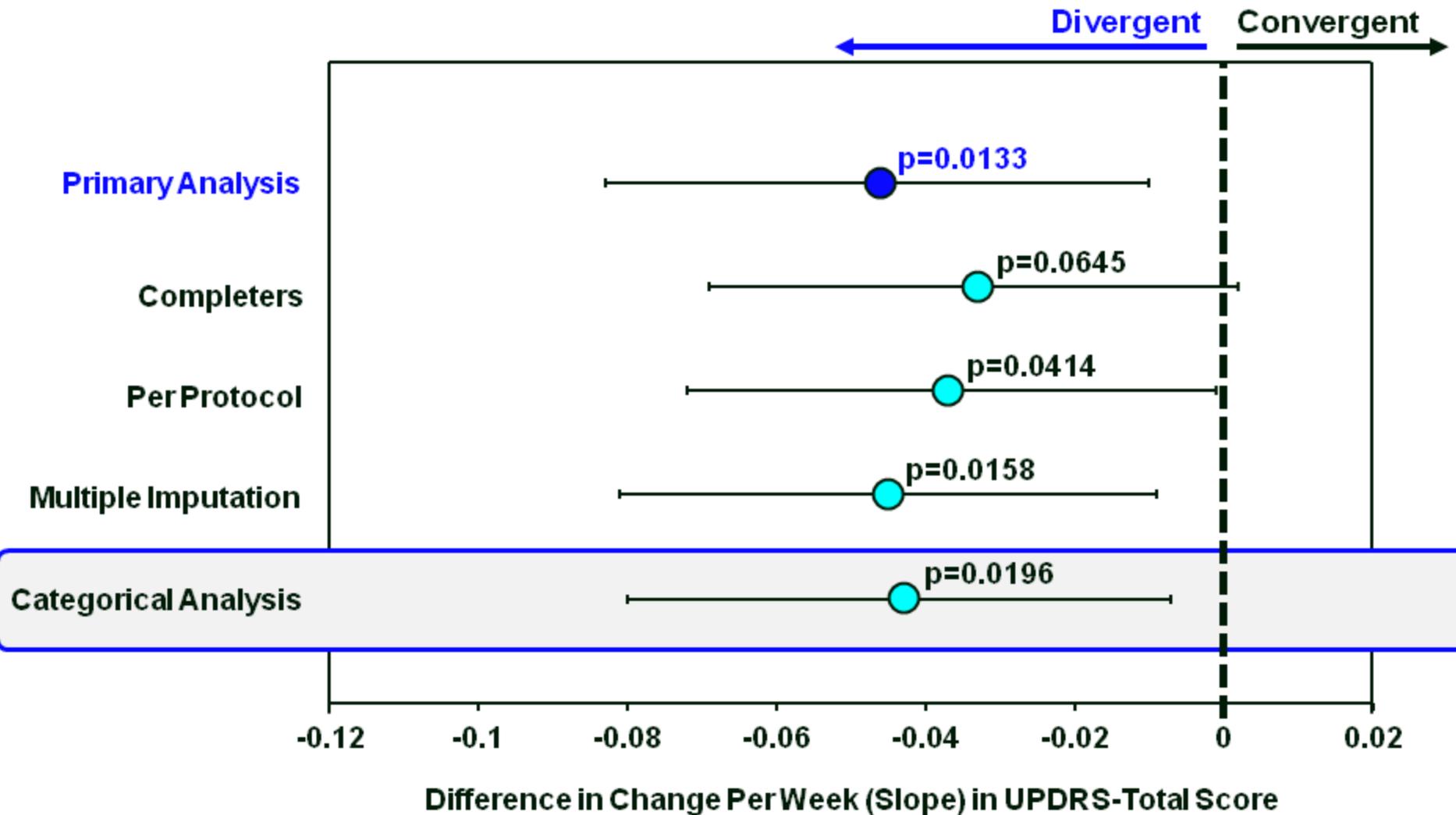


Schematic illustration

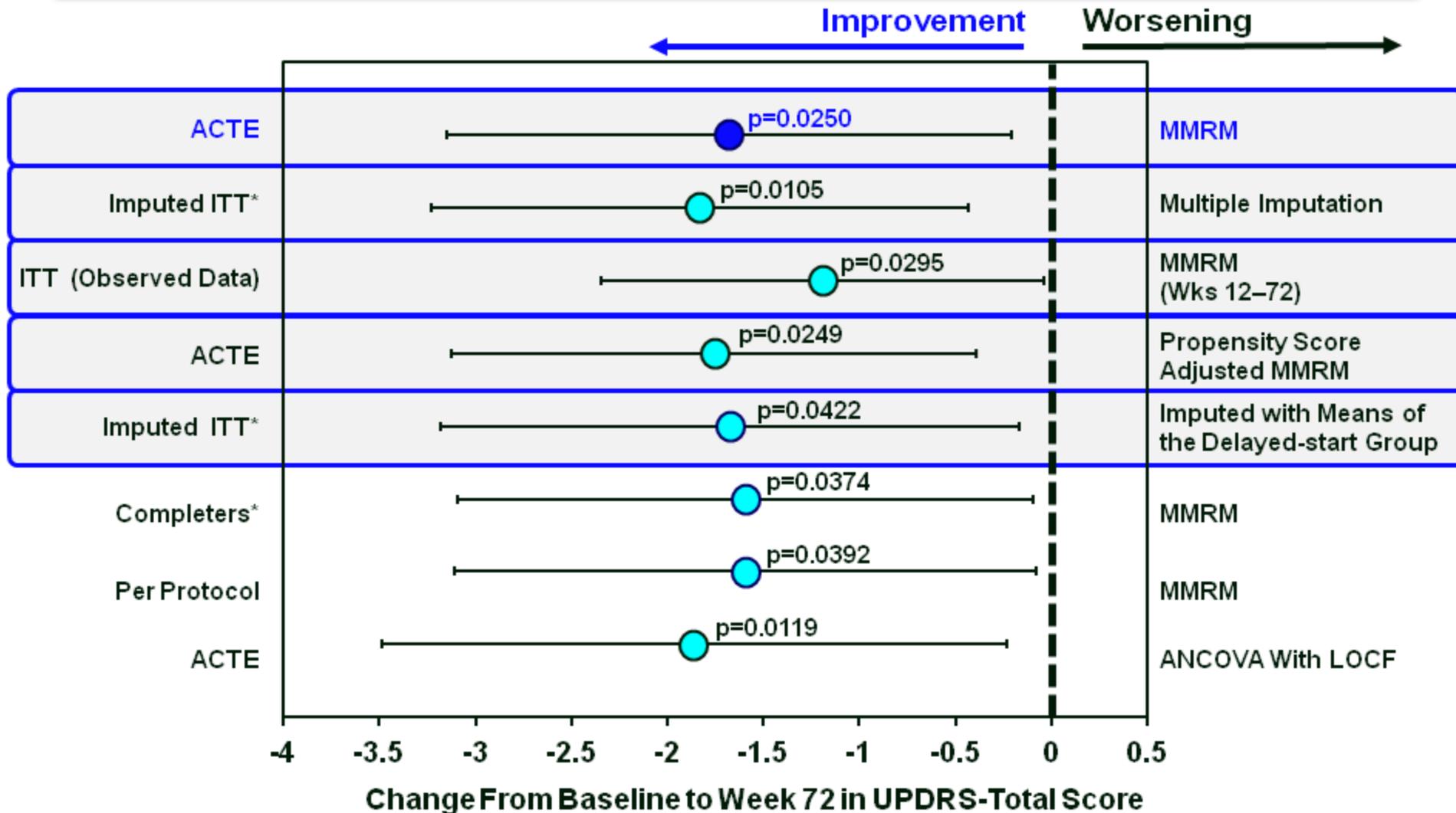
Delayed-start Design Study Issues

- 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

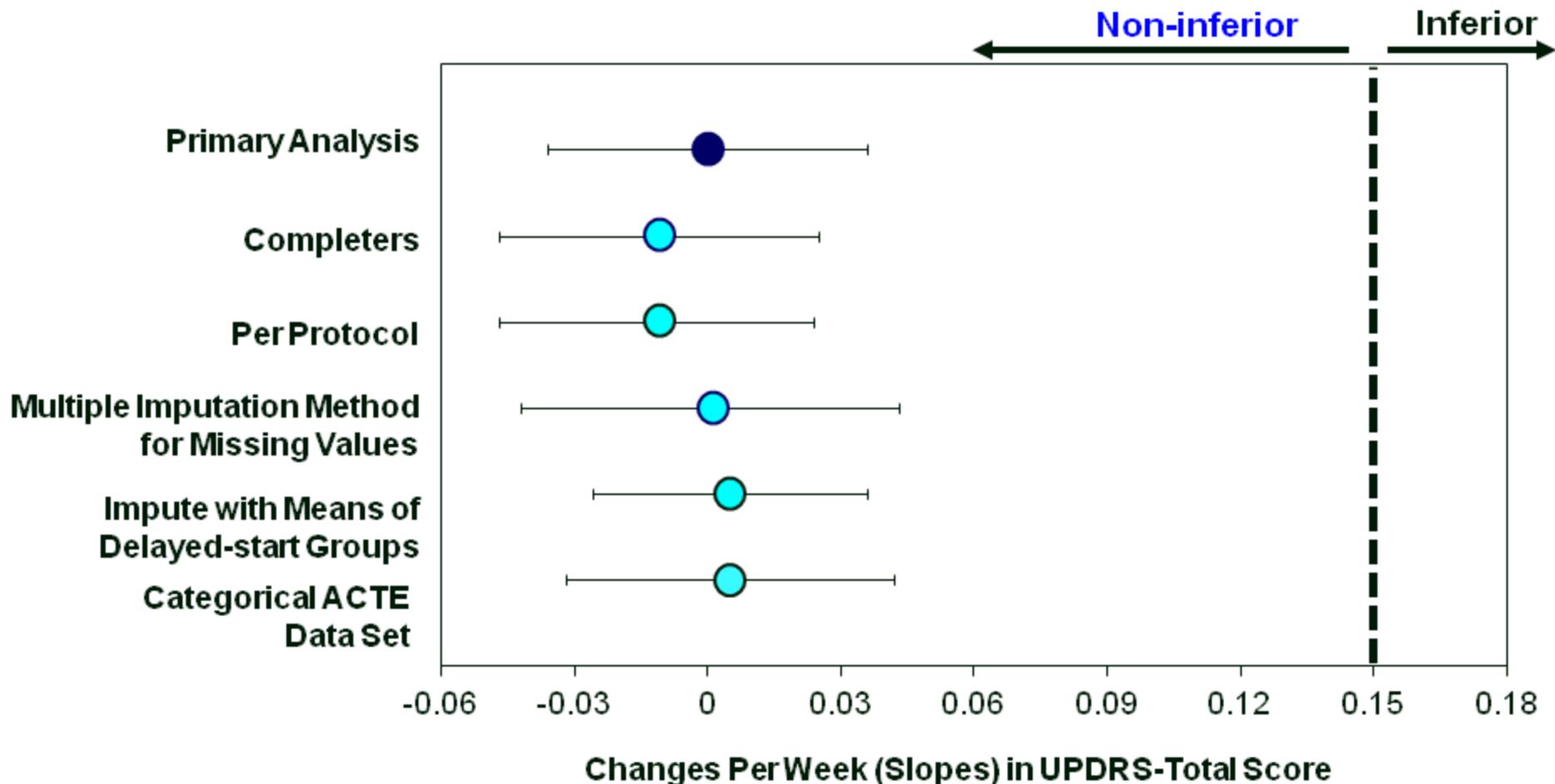


ADAGIO: Consistent Results Demonstrated for 1mg Dose in Endpoint II



*Predefined sensitivity analysis

ADAGIO: Consistent Results Demonstrated for 1 mg Dose in Endpoint III

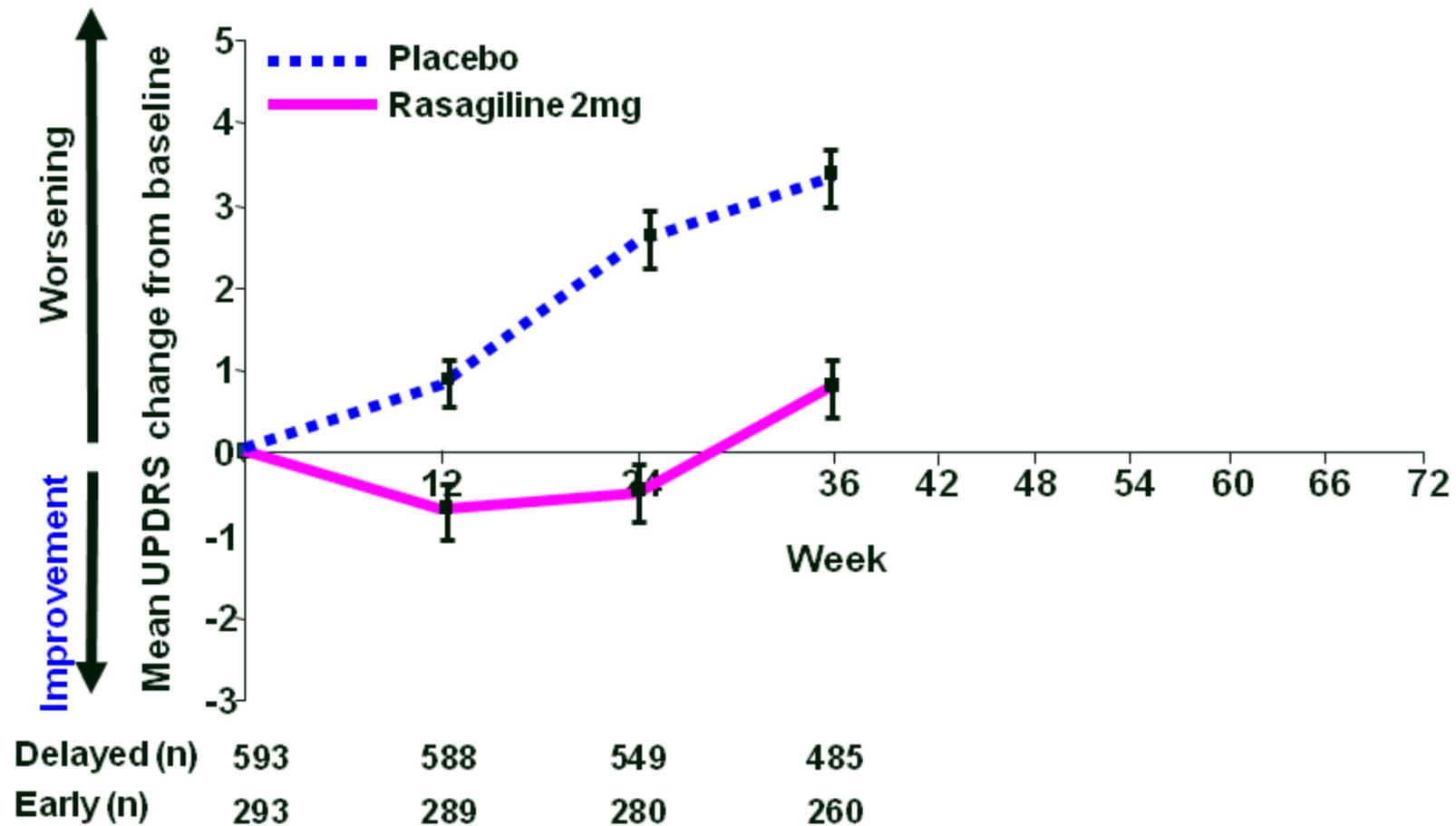


ADAGIO: Rasagiline 1mg Dose Results Support Slowing of Clinical Progression

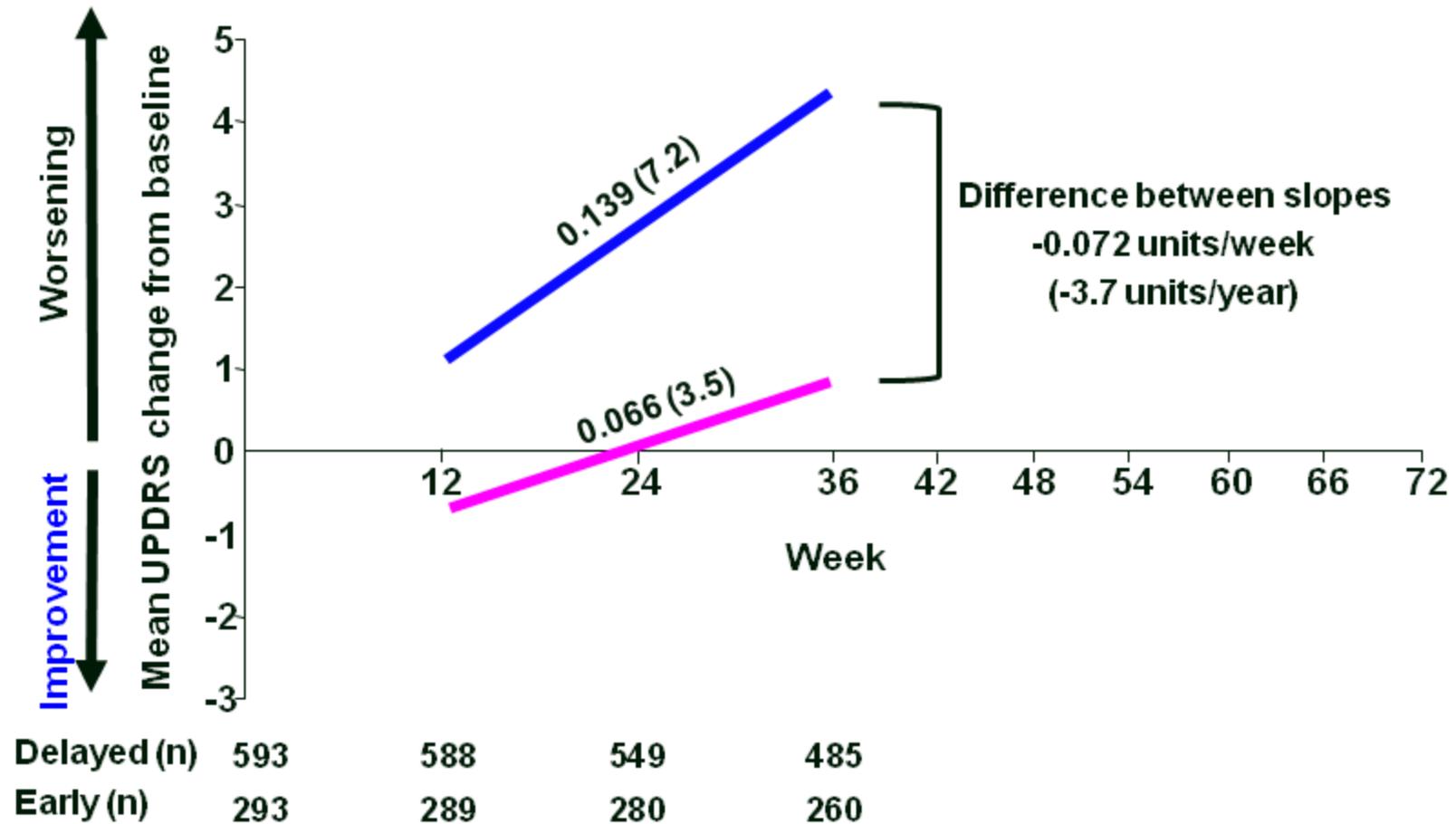
- Results from three primary endpoints support slowing of clinical progression
- Further supported by various imputation strategies and sensitivity analyses for all endpoints

ADAGIO 2mg

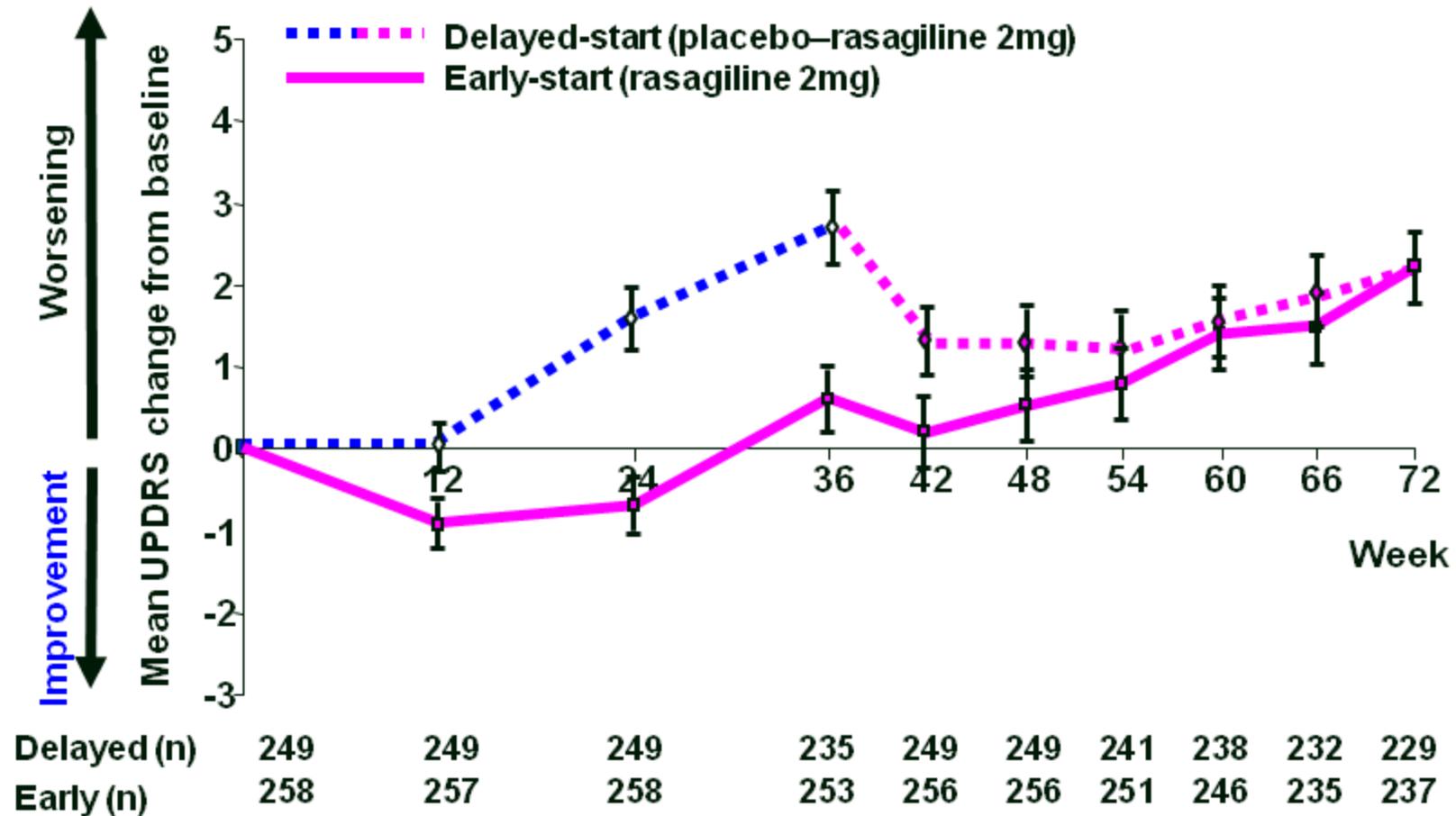
ADAGIO: Rasagiline 2mg Observed Data for Modified ITT Cohort (Weeks 0-36)



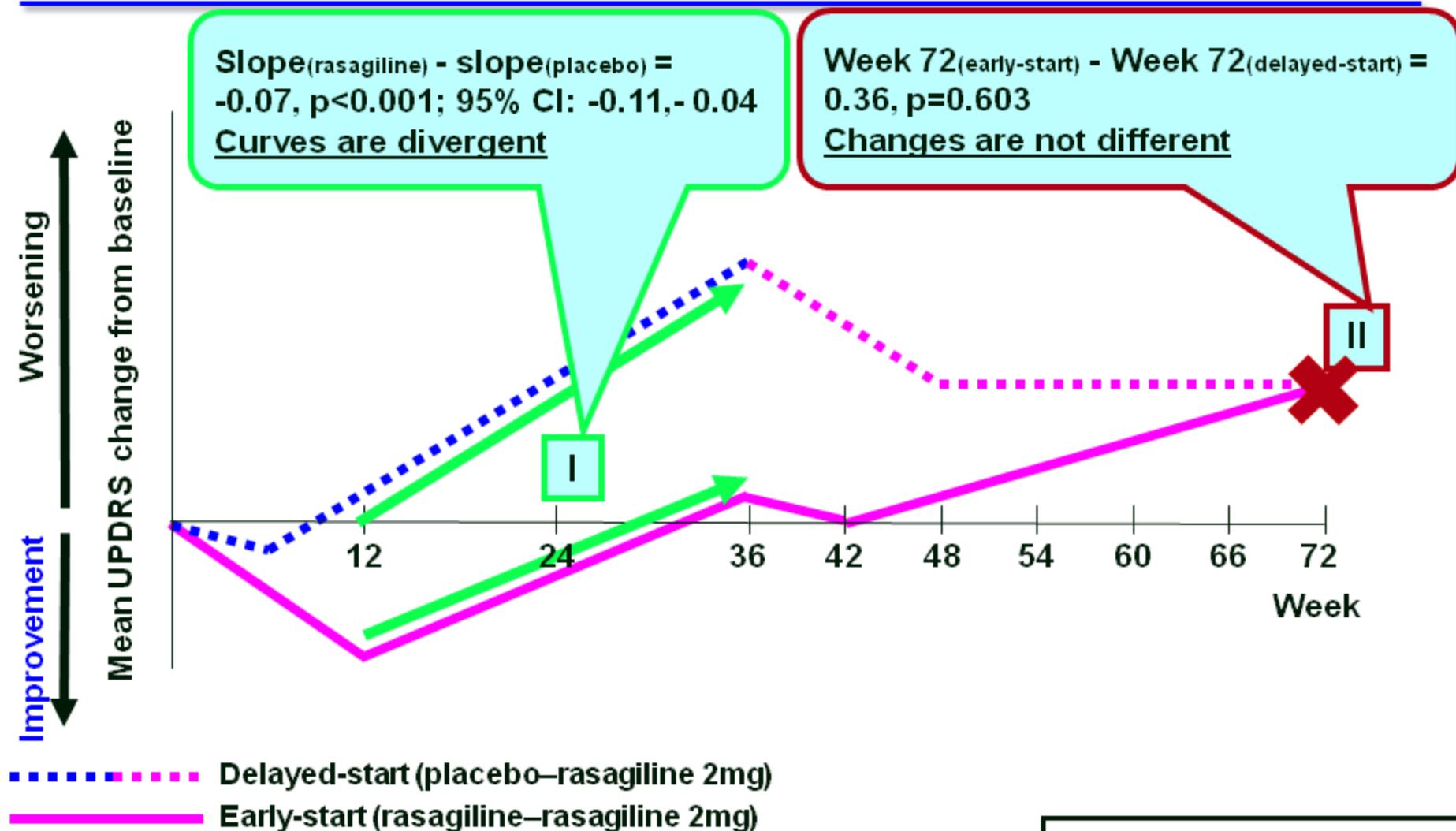
ADAGIO: Rasagiline 2mg Observed Data for Modified ITT Cohort (Weeks 0-36)



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



ADAGIO: Rasagiline 2mg Dose Did Not Meet Endpoint II



Schematic illustration

Possible Explanations for ADAGIO 2mg Results on Endpoint II

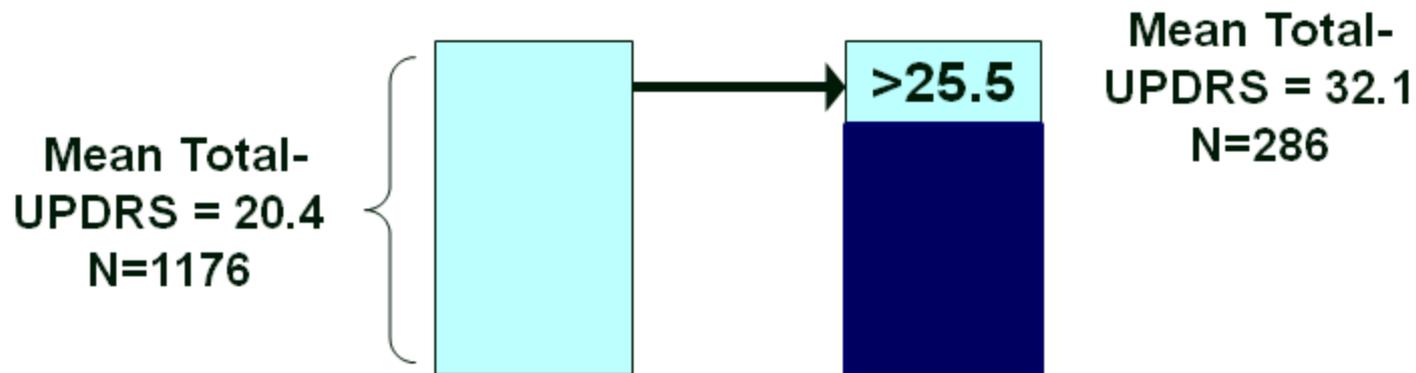
- Chance
- Different pharmacology
- Impact of early transfers
- Lower sensitivity to detect change in UPDRS scale in milder patients

Patients at Baseline More Advanced in TEMPO than in ADAGIO

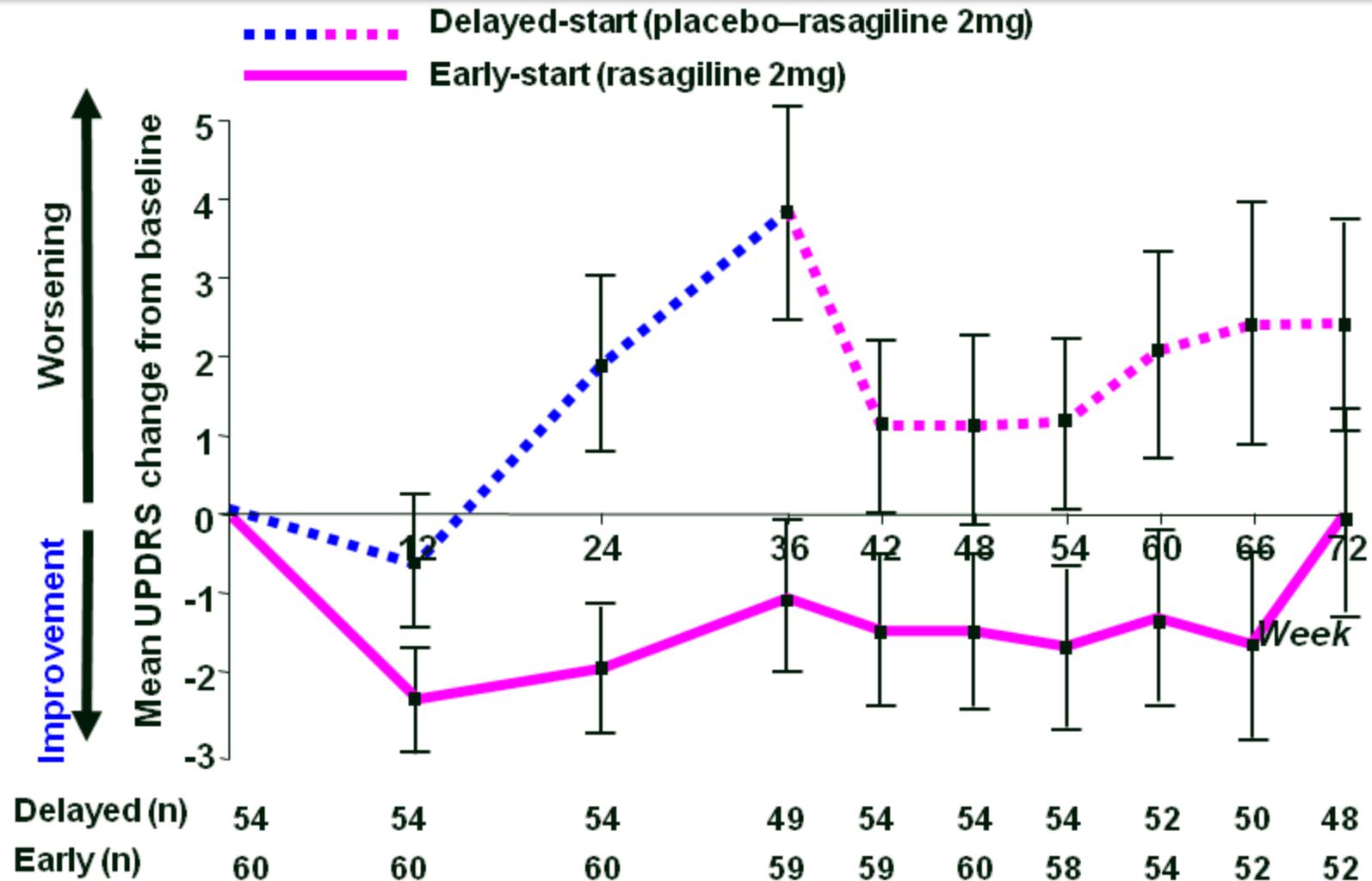
	TEMPO	ADAGIO
Patients randomized (n)	404	1,176
Male patients (n, %)	257 (63.6%)	718 (61.1%)
Age, years (mean, SD)	60.8 (10.8)	62.2 (9.6)
PD duration, months (mean, SD)	12.1 (13.2)	4.5 (4.6)
UPDRS-Total score (mean, SD)	25.0 (10.8)	20.4 (8.5)
UPDRS-Motor score (mean, SD)	17.8 (8.43)	14.2 (6.4)
Modified Hoehn & Yahr (mean, SD)	1.9 (0.5)	1.5 (0.5)

ADAGIO: Rasagiline 2mg Was Assessed in Subjects with Highest BL UPDRS Scores

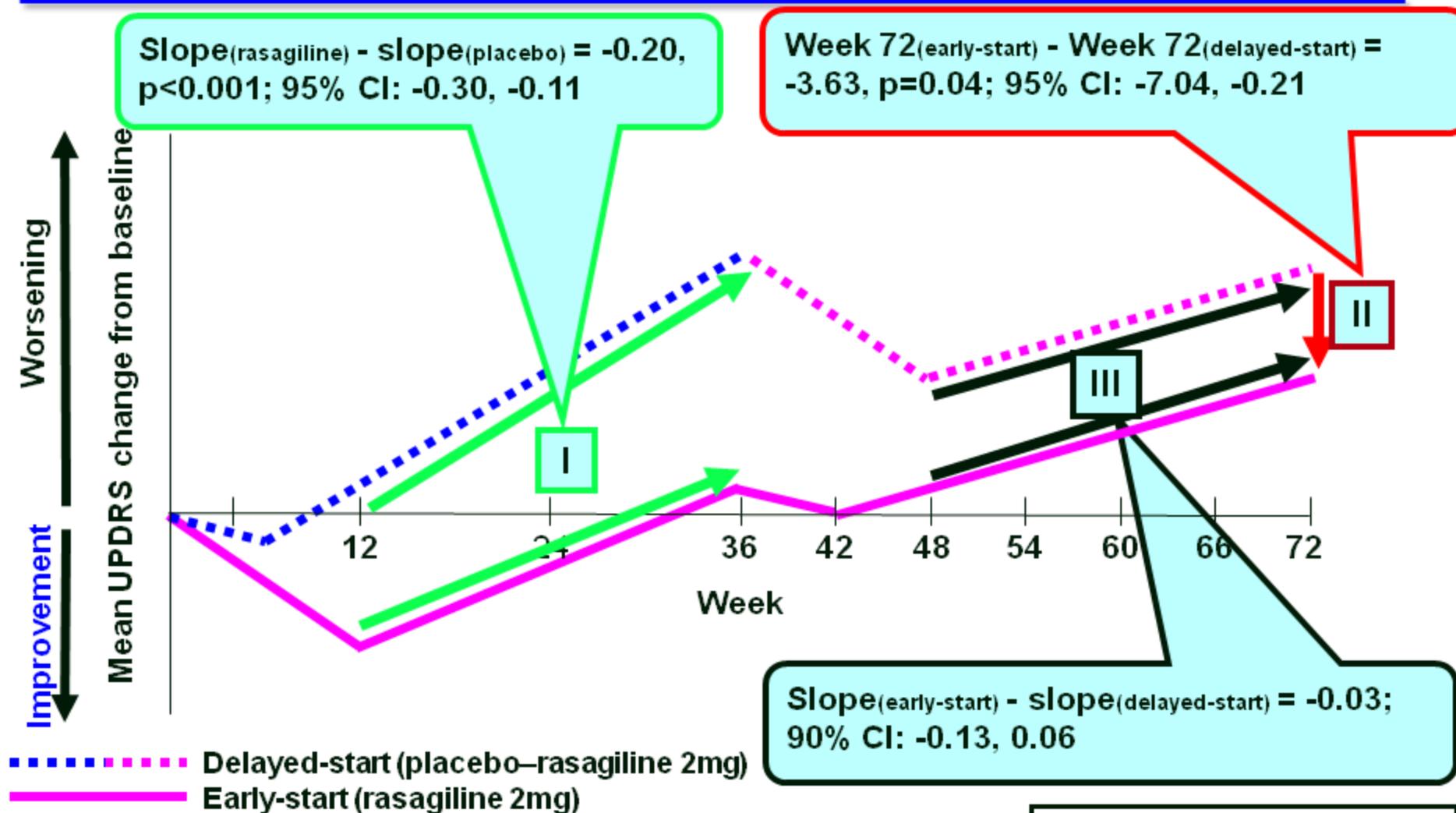
- A post-hoc analysis was conducted in subjects with highest baseline Total-UPDRS scores (>25.5)



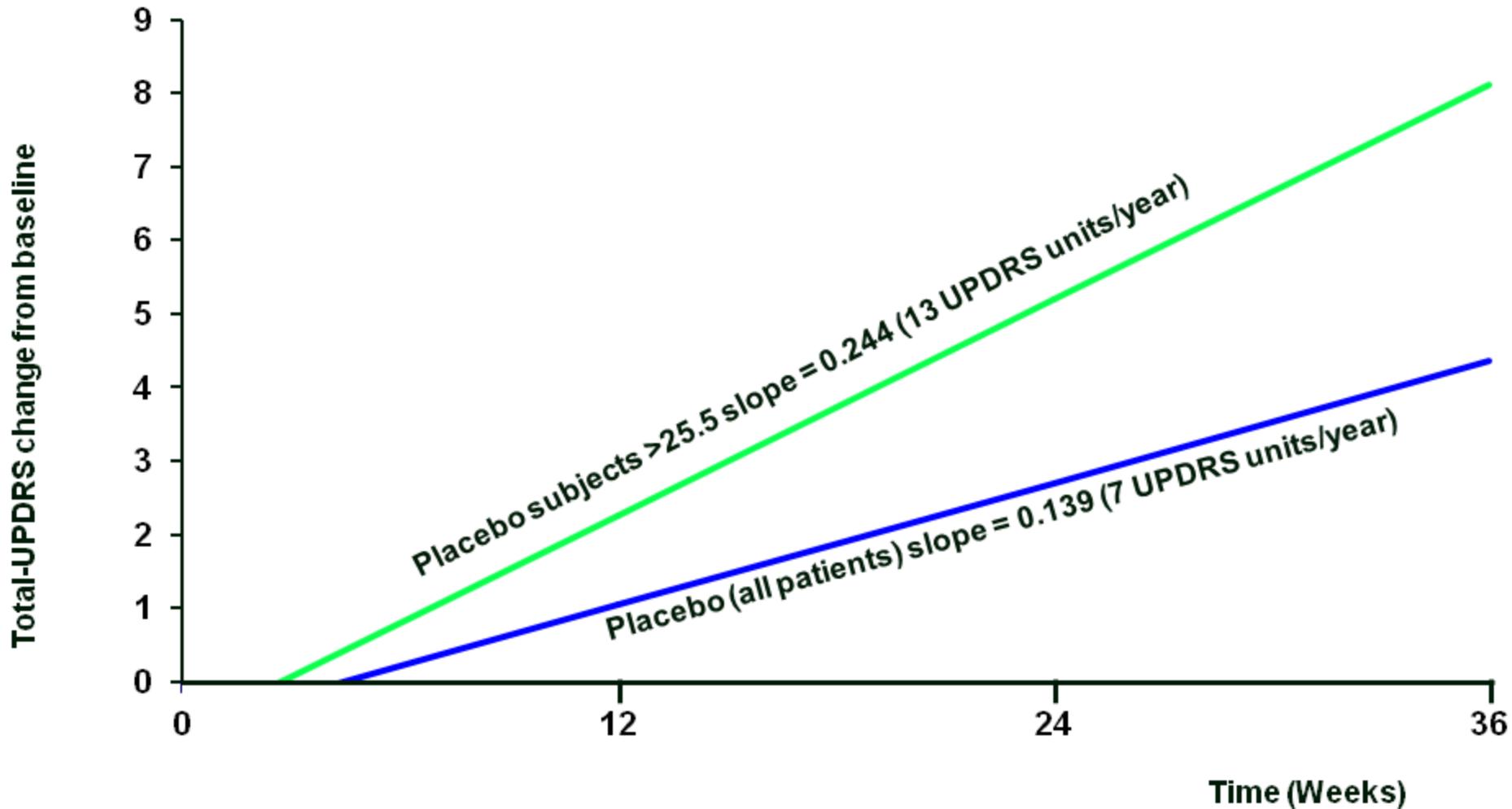
ADAGIO: Highest Baseline UPDRS Scores (>25.5) – Rasagiline 2 mg



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



ADAGIO: Rates of UPDRS Progression for Placebo Subjects



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

Placebo-controlled Phase	Placebo (n=593) %	Rasagiline 1mg (n=288) %	Rasagiline 2mg (n=293) %
Incidence of AEs	68.0	65.3	68.3
Incidence of SAEs	3.7	4.2	4.4
Discontinuations associated with AEs	2.9	3.1	3.4

ADAGIO: No Apparent Relationship Between Dose and Rate of Adverse Events

Placebo-controlled Phase	Placebo (n=593) %	Rasagiline 1mg (n=288) %	Rasagiline 2mg (n=293) %
Fatigue	2.9	5.9	3.4
Constipation	3.2	4.9	2.4
Arthralgia	4.0	3.8	4.4
Dizziness	3.2	3.5	4.1
Fall	3.9	3.1	4.8
Musculoskeletal Pain	3.4	2.1	4.4

ADAGIO: Dopaminergic AEs Similar in Rasagiline and Placebo

Placebo-controlled Phase	Placebo (n=593) %	Rasagiline 1mg (n=288) %	Rasagiline 2mg (n=293) %
Nausea/vomiting	3.9	4.2	2.7
Hypertension	3.9	1.7	2.4
Somnolence	1.5	0.7	2.1
Orthostatic hypotension	0.8	0.7	0.3
Hallucination	0.2	-	0.3
Hypersexuality	-	-	0.3

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

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

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

The AAPS Journal, Vol. 11, No. 3, September 2009 (© 2009)
DOE: 10.1208/s12248-009-9123-2

Research Article

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

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Received 8 December 2008; 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 four 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 features 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.

Movement Disorders
Vol. 00, No. 00, 2008, pp. 000-000
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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 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 Eidad Melamed, MD,⁹ Eli Eyal, PhD,¹⁰ and Olivier Rascol, MD¹¹

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³Department of Neurology, Baylor College of Medicine, Houston, Texas, USA

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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, IRCCS San Raffaele Pisana, Rome, Italy

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

¹⁰Global Statistics Unit, Teva Pharmaceutical Industries Ltd, Israel

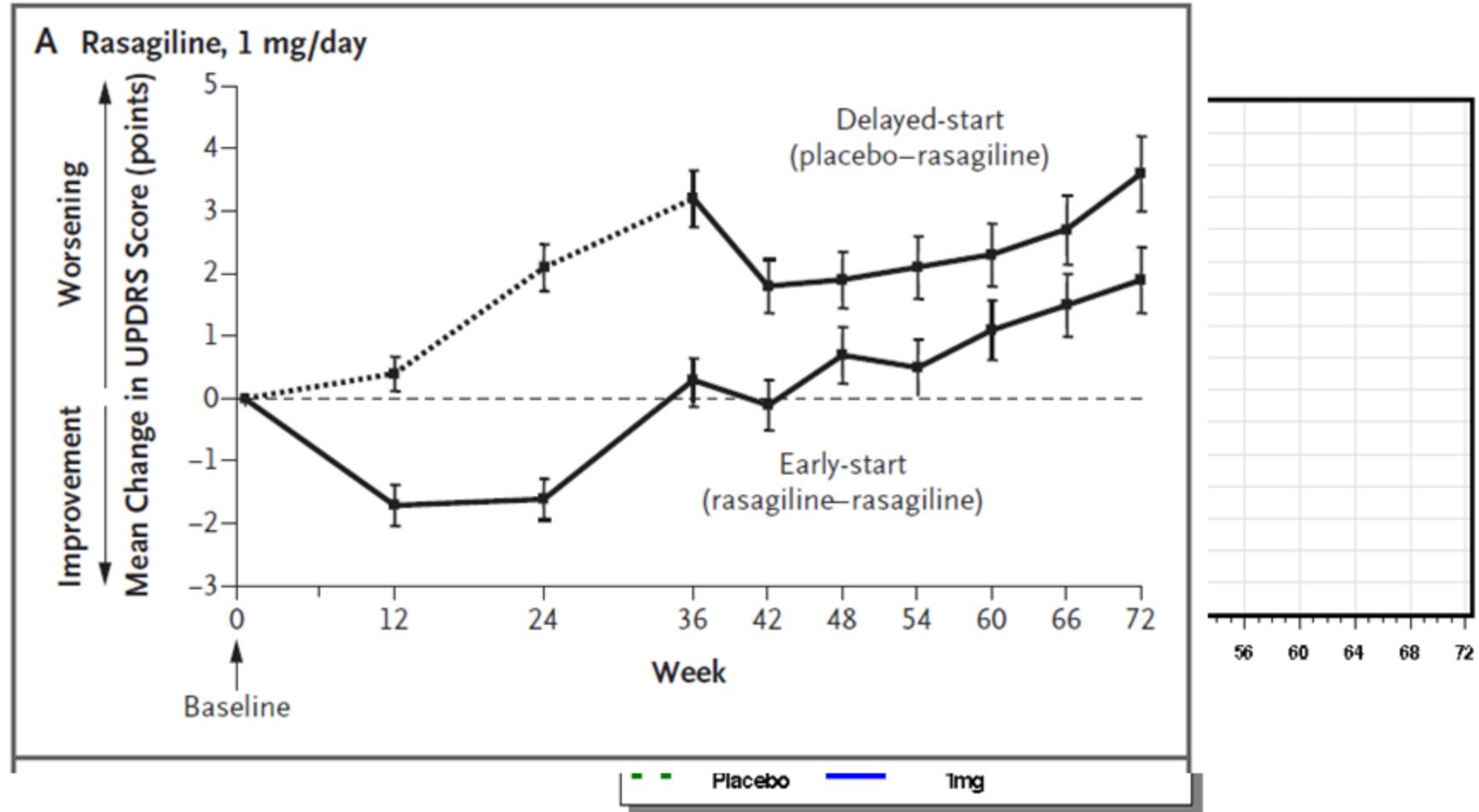
¹¹INSERM U455, Clinical Investigation Center and Departments of Clinical Pharmacology and Neurosciences, Faculté de Médecine, Toulouse, France

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 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

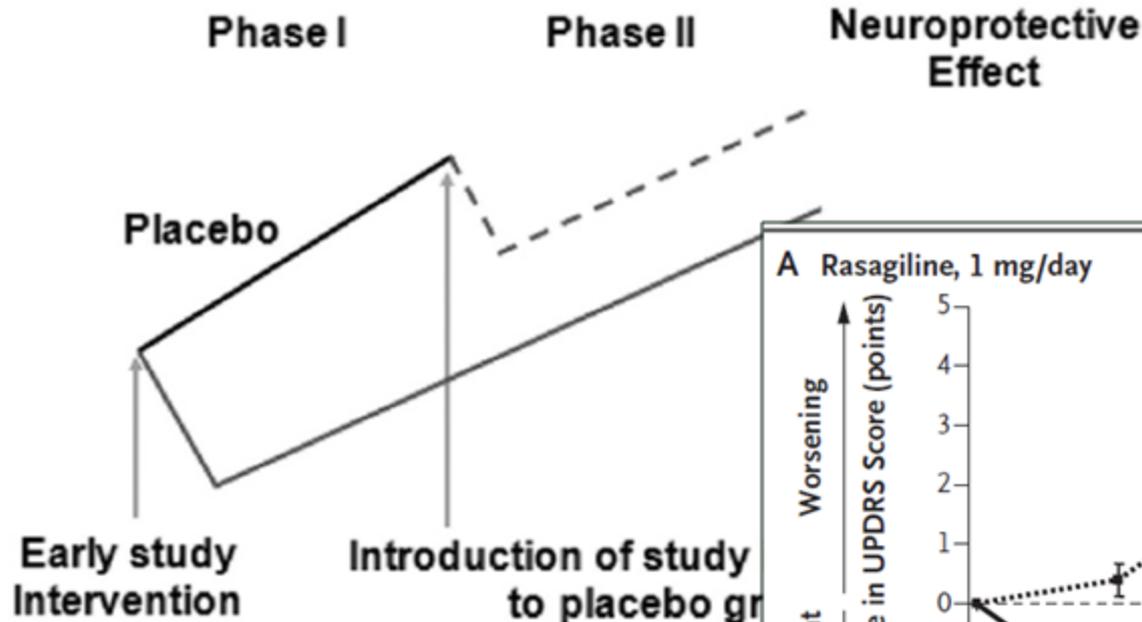
ADAGIO Study Rasagiline 1mg



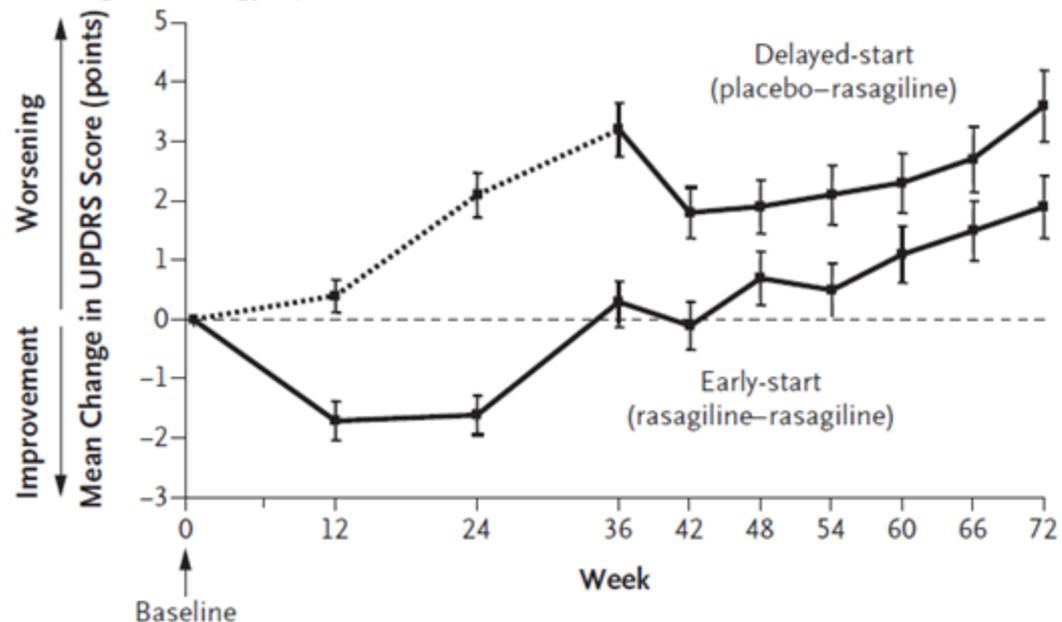
Positive Delayed Start Study

FDA Model vs ADAGIO - Rasagiline 1mg

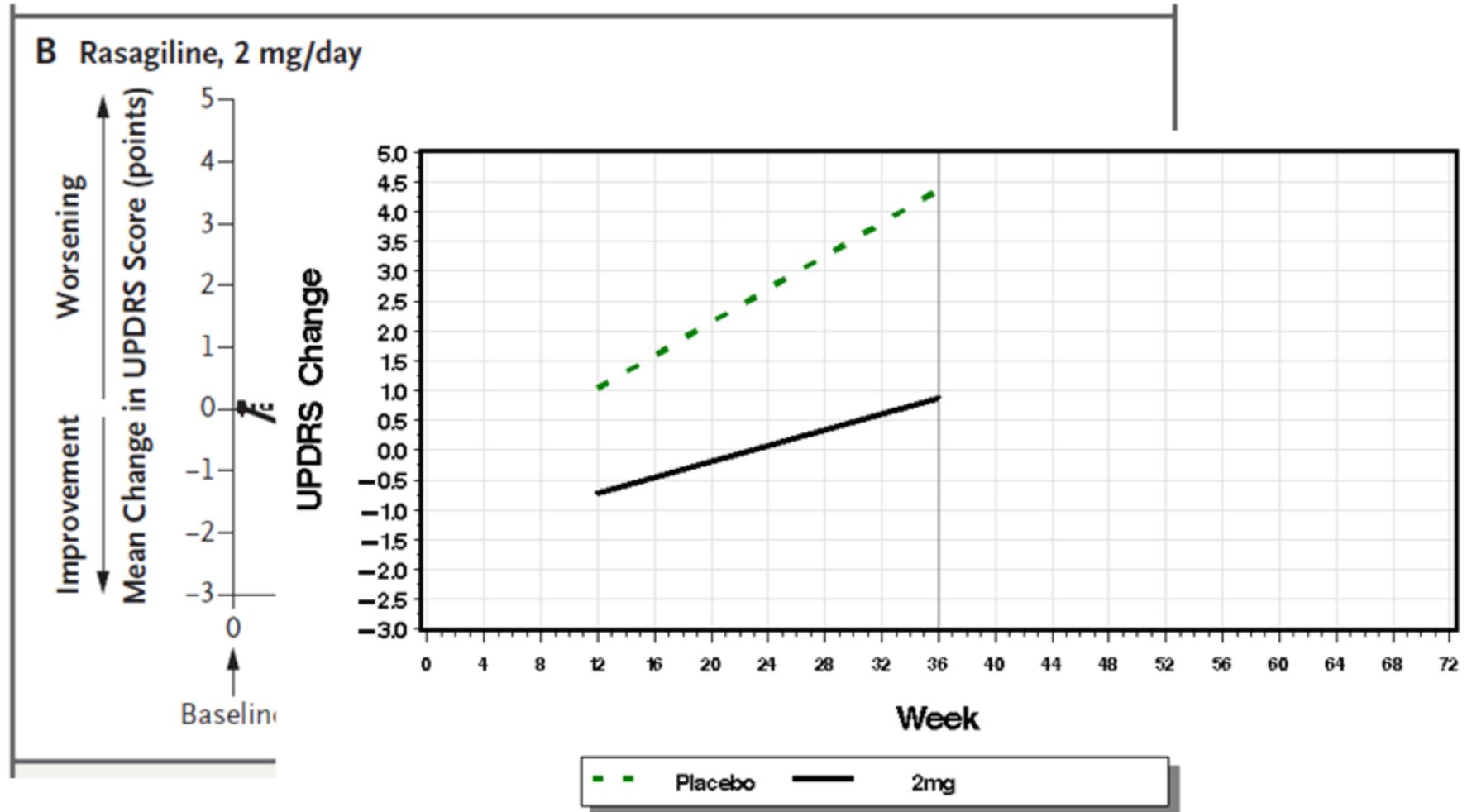
Randomized Start Design



A Rasagiline, 1 mg/day



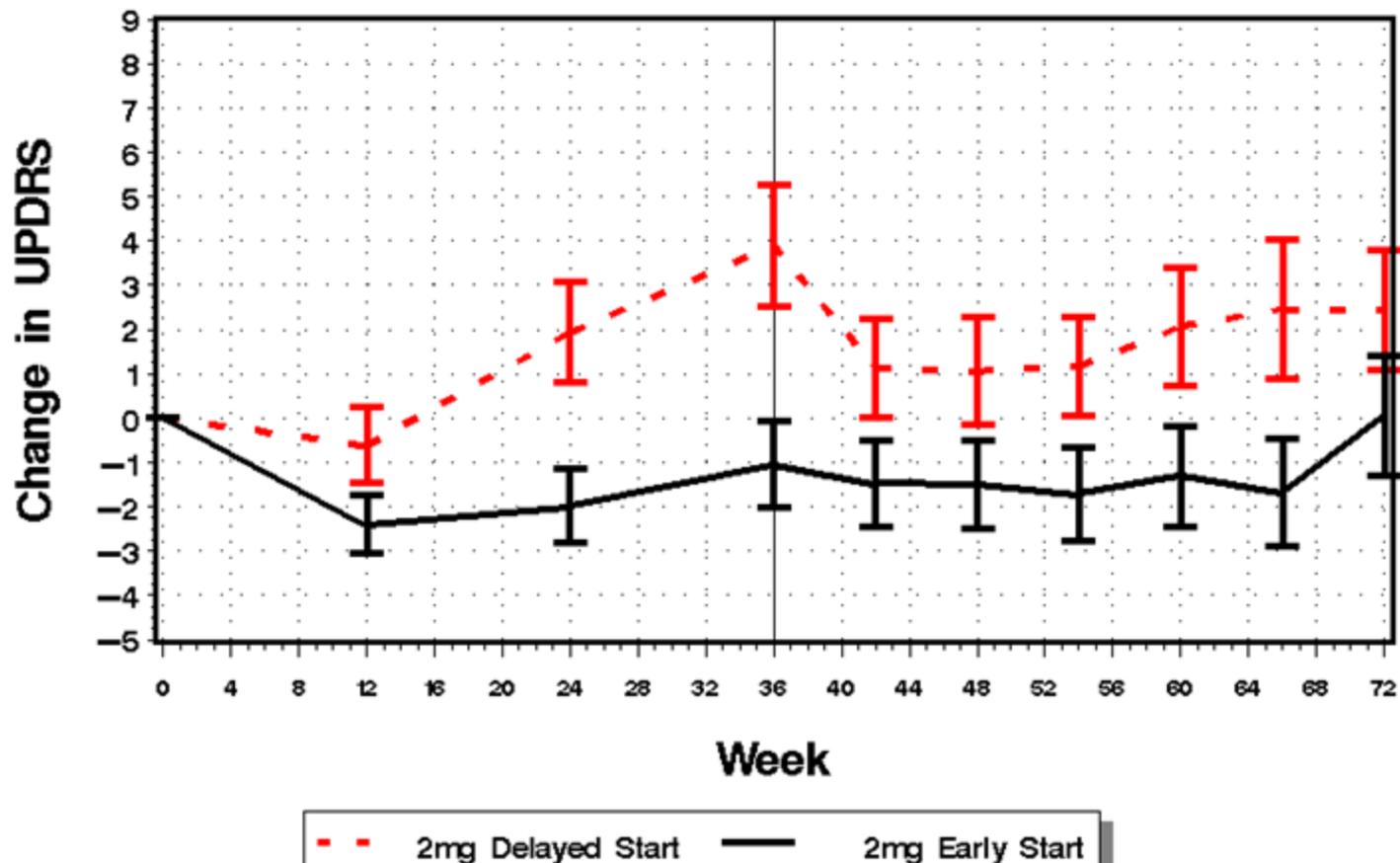
ADAGIO Study Rasagiline 2mg



Rasagiline 2 mg/day Upper Quartile Analysis

TVP-1012/500 (ADAGIO)

Change in UPDRS (Mean \pm SE) - ACTE Data Analysis Set-2mg-Baseline UPDRS GT 25.5



ADAGIO: Further Results Published in Lancet Neurology

Articles

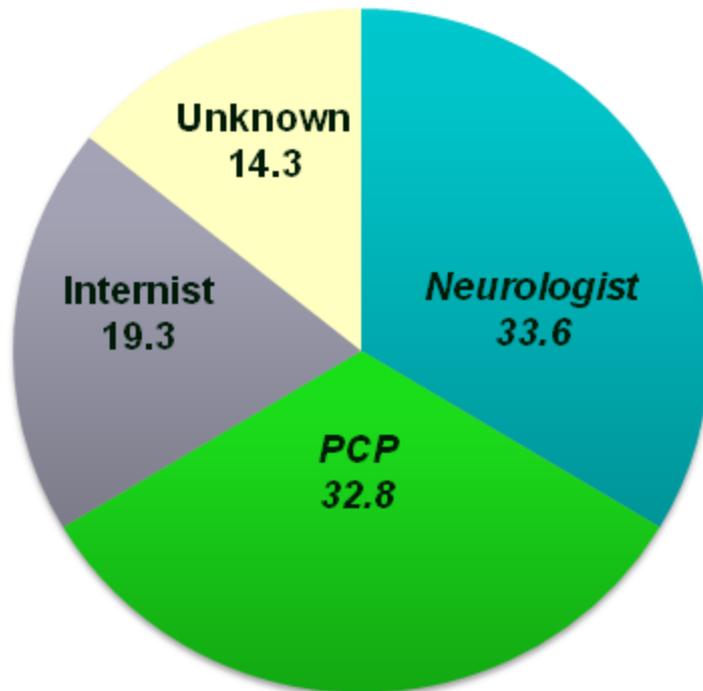
A double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study): prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes



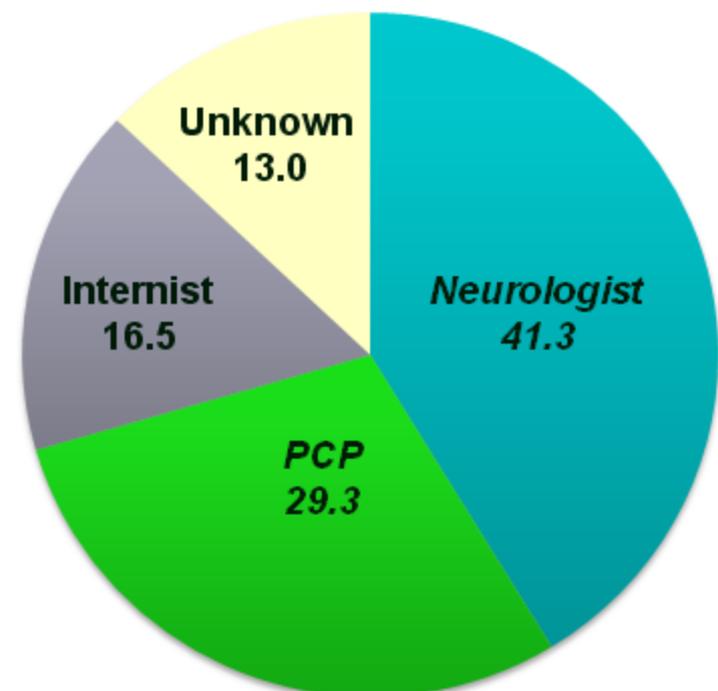
Olivier Rascol, Cheryl J Fitzer-Attas*, Robert Hauser, Joseph Jankovic, Anthony Lang, J William Langston, Eldad Melamed, Werner Poewe, Fabrizio Stocchi, Eduardo Tolosa, Eli Eyal, Yoni M Weiss, C Warren Olanow**

Breakdown of Physicians Prescribing Medications for PD 2007

Percent writing prescriptions for *de novo* patients (n=19,673)



Percent writing prescriptions for all patients (n=29,682)



Rasagiline for Slowing Clinical Progression in Parkinson's Disease

Teva Pharmaceuticals

PCNSDAC

October 17, 2011

Backup Slides Shown

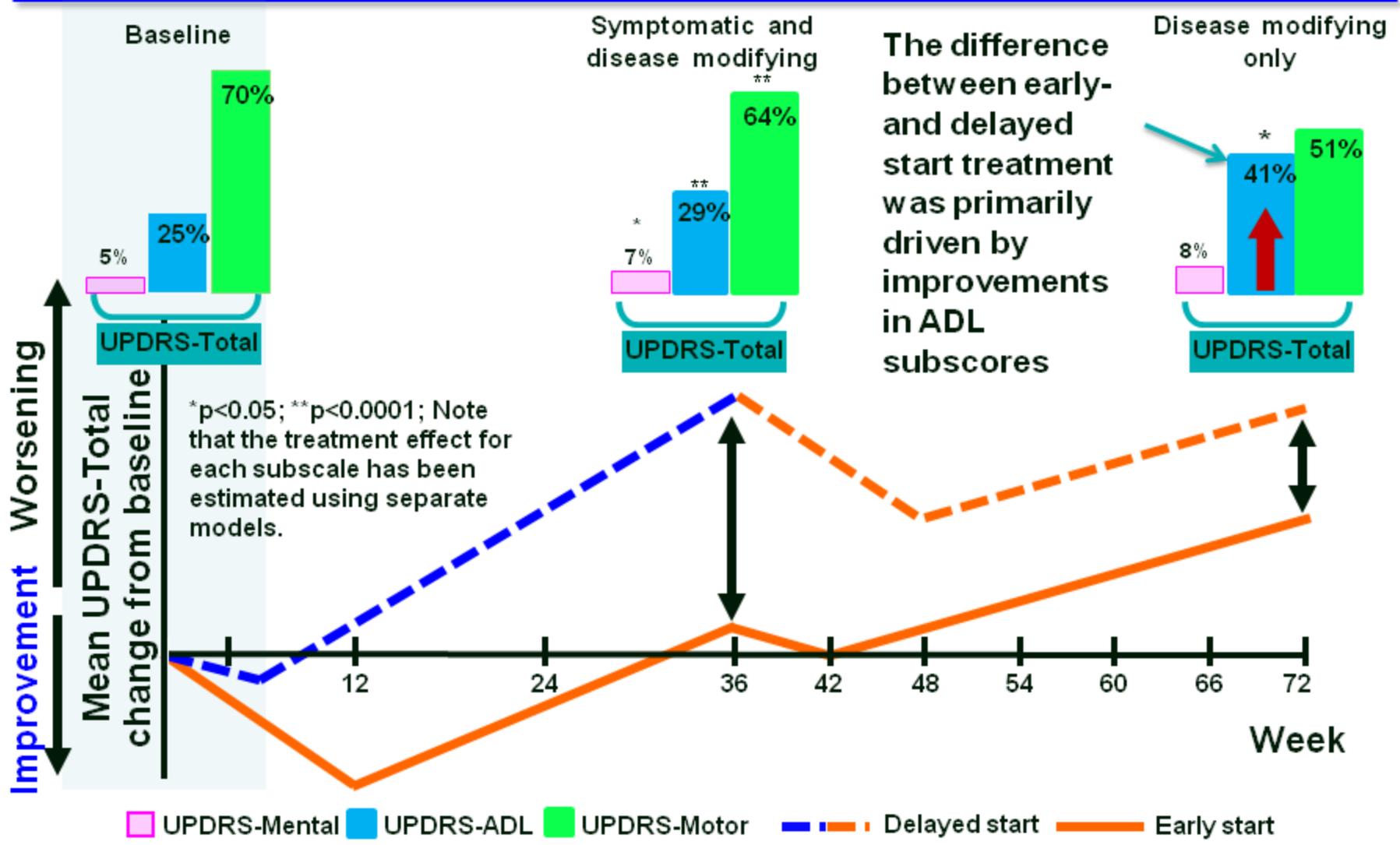
Significance of the Dose Level Interactions

- Dose level by center interaction: $p=0.0125$
- Dose level by baseline UPDRS interaction: $p=0.0481$

Nature of Dose Level Interactions

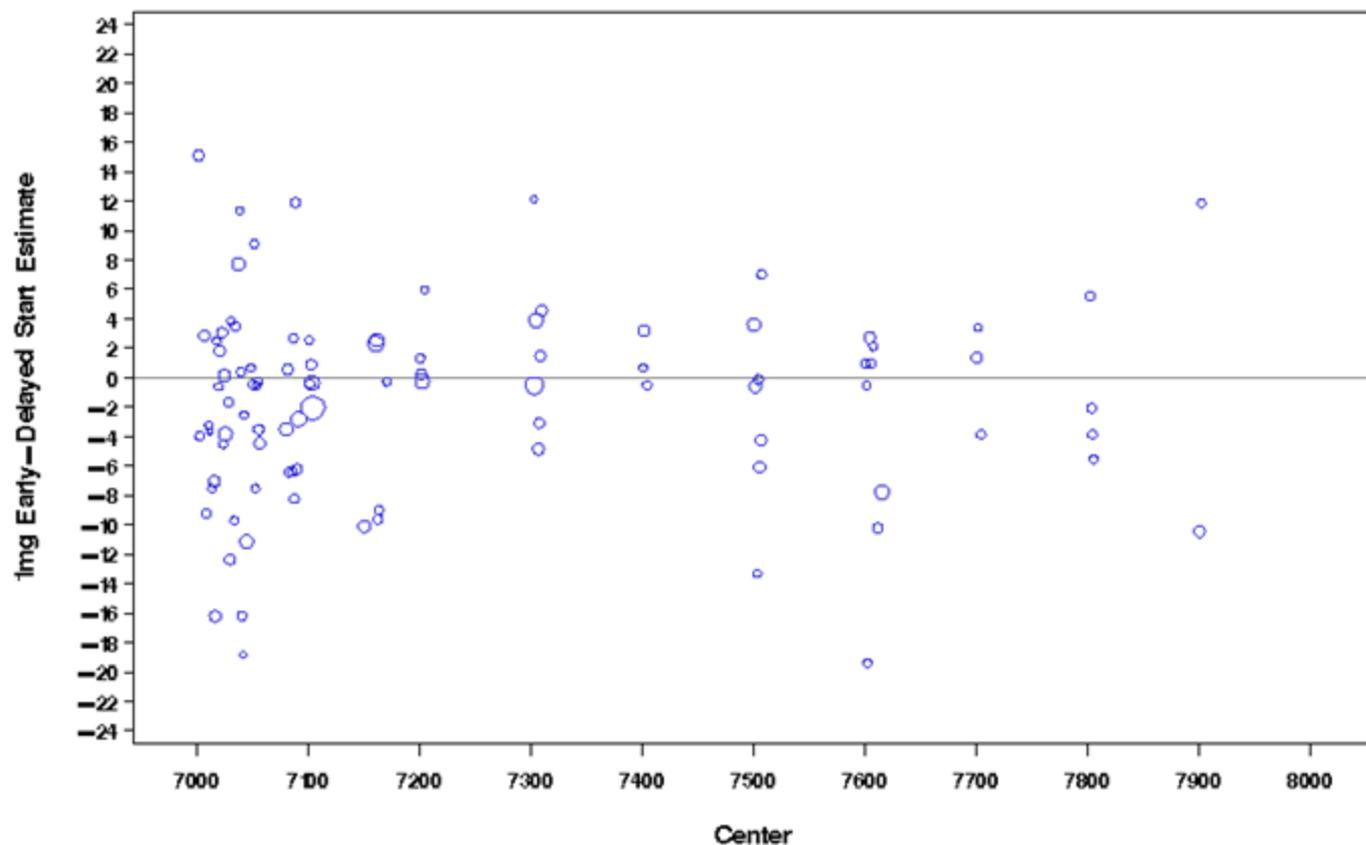
- Based on the combined dataset with model including dose-level interactions:
- Baseline UPDRS coefficients for each dose level:
- 1 mg dose-level coef.(SE): 0.047 (0.036); $p=0.19$
- 2 mg dose-level coef. (SE): -0.053 (0.036);
 $p=0.13$
- Difference (1mg vs 2mg dose-level): 0.1 (0.05)
 $p=0.048$

Relative Contribution of UPDRS-Mental, ADL, and Motor Sub-scores to UPDRS Baseline, and Treatment effects (1mg Rasagiline)

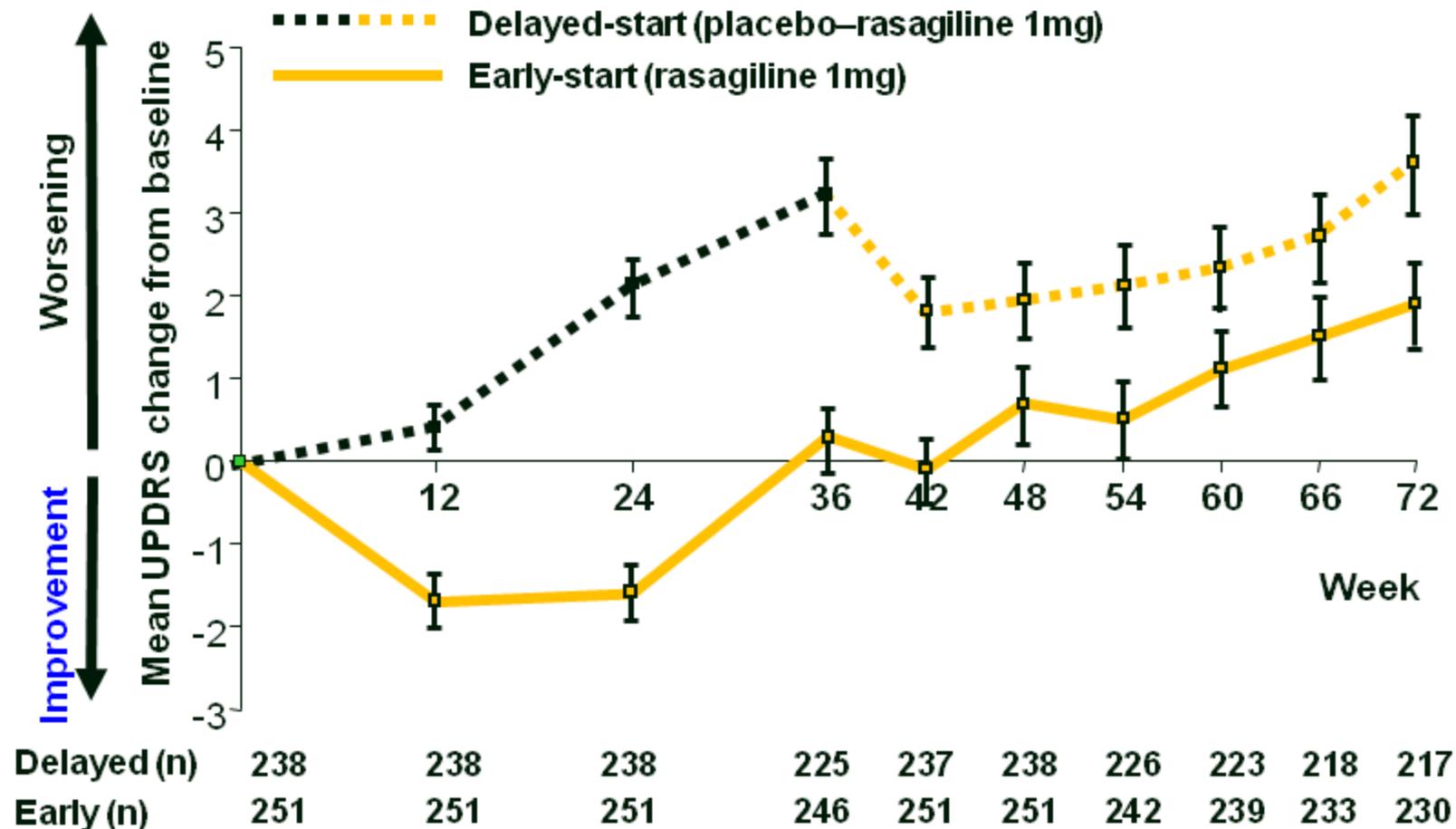


Separate Dataset 1 mg: Treatment by Center Interaction

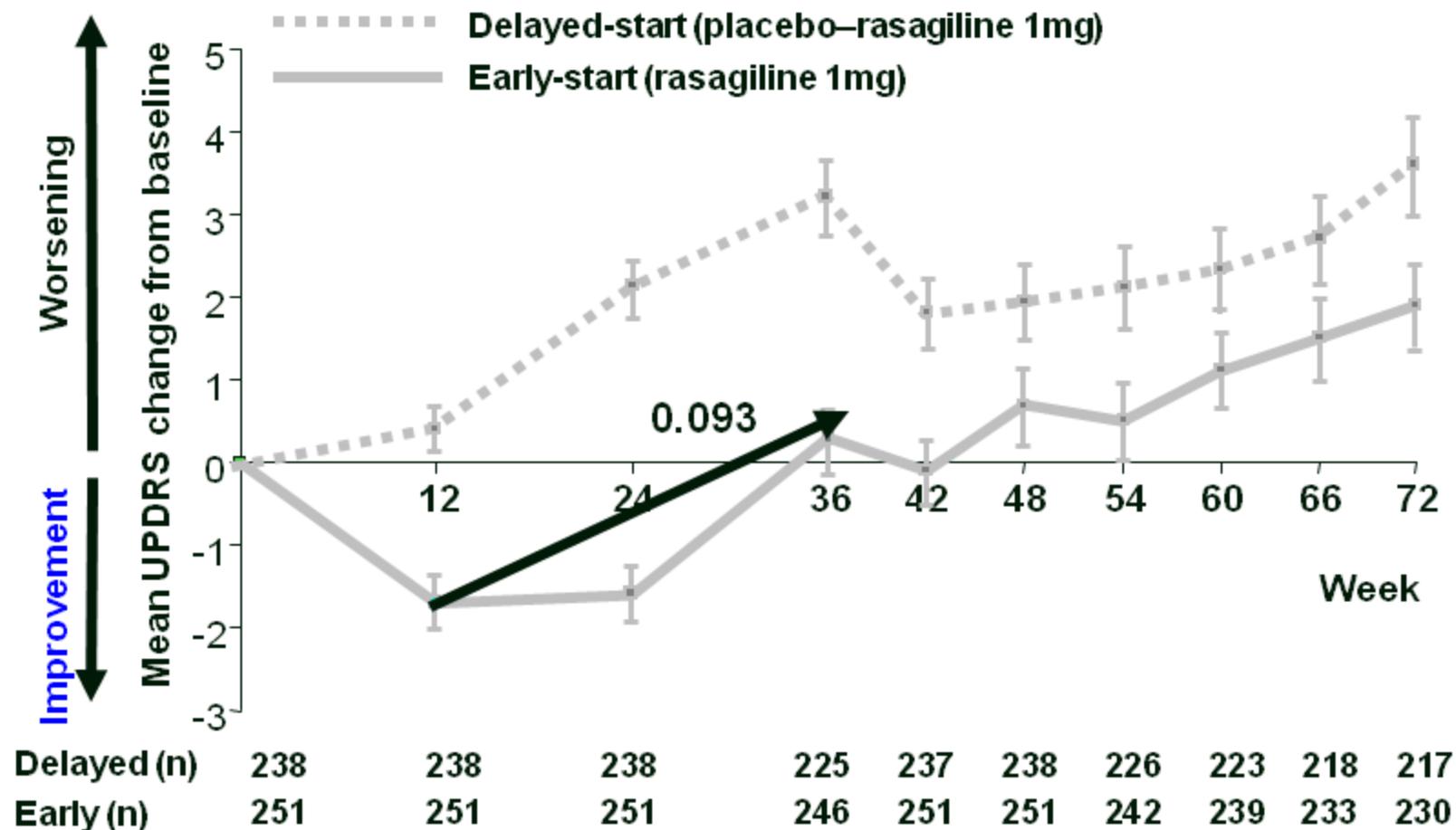
ADAGIO — Active Phase — Separated 1mg Data Set
Estimates of Early-Delayed Start within Center (Mean across Visits)
P-Value of Treatment by Center Interaction = 0.0044
Circle size is proportional to the number of subjects in each Center



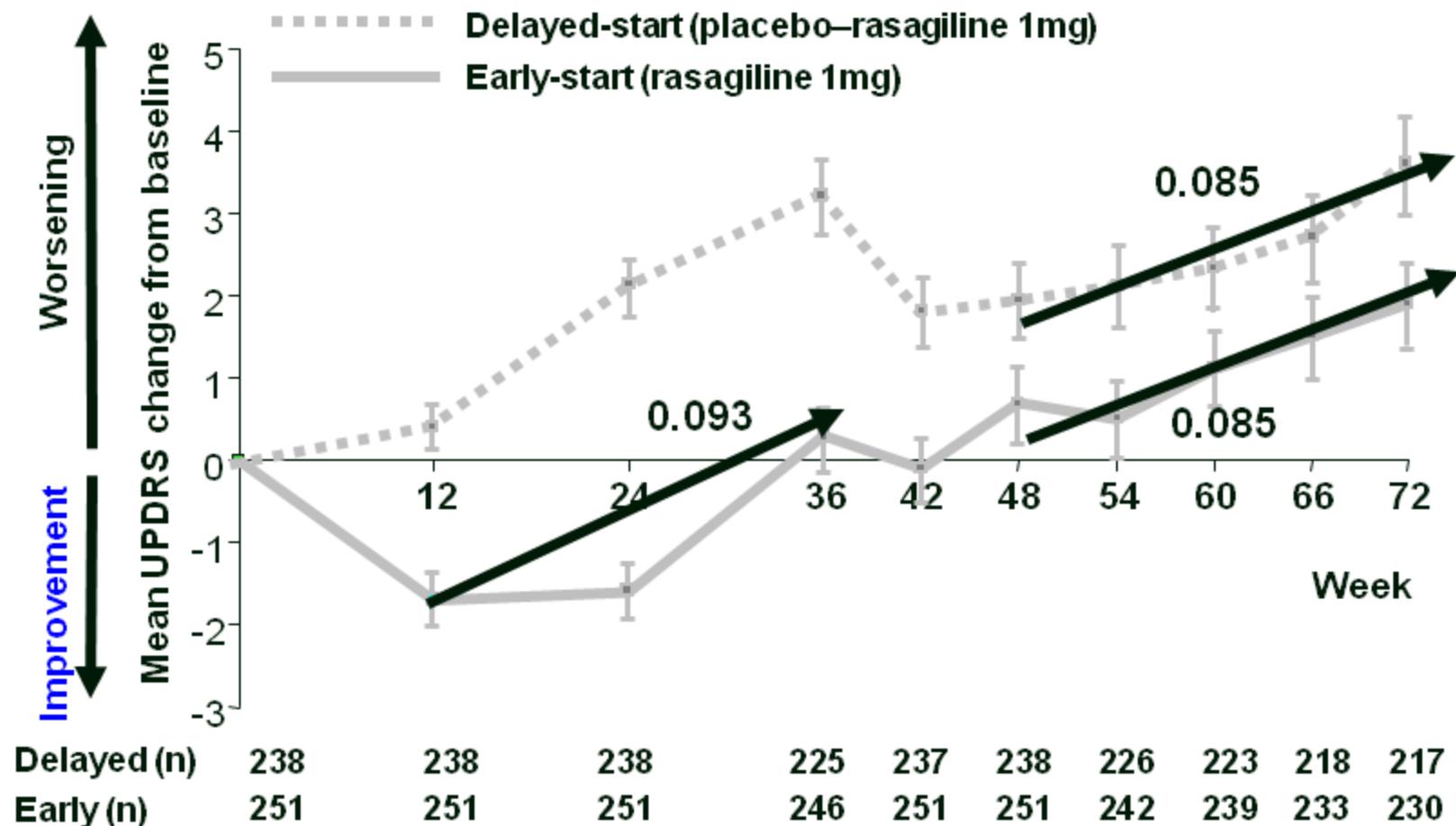
ADAGIO: Rasagiline 1mg Observed Data for ACTE Cohort (Weeks 0-72)



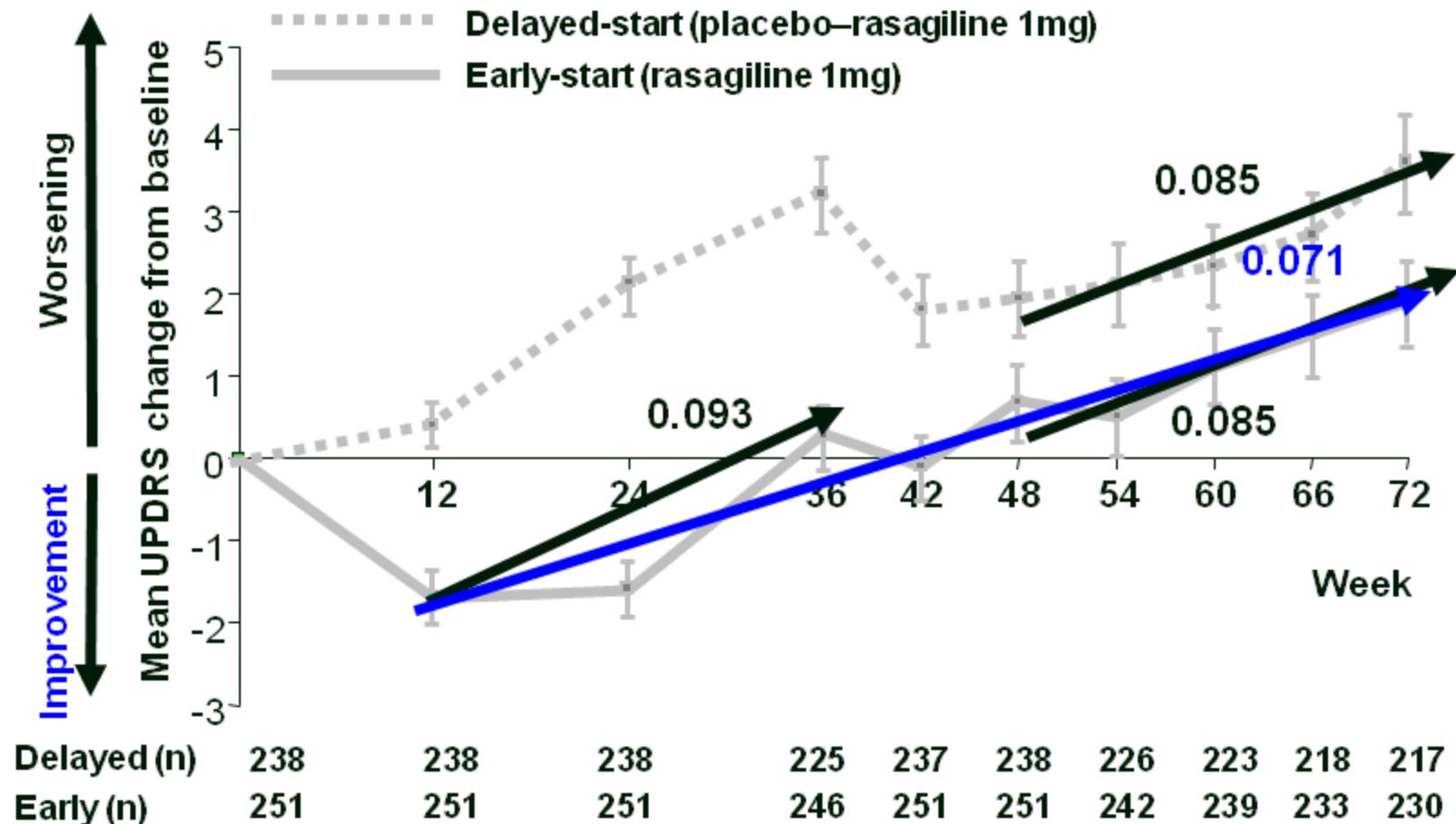
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ADAGIO: Rasagiline 1mg Observed Data for ACTE Cohort (Weeks 0-72)



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

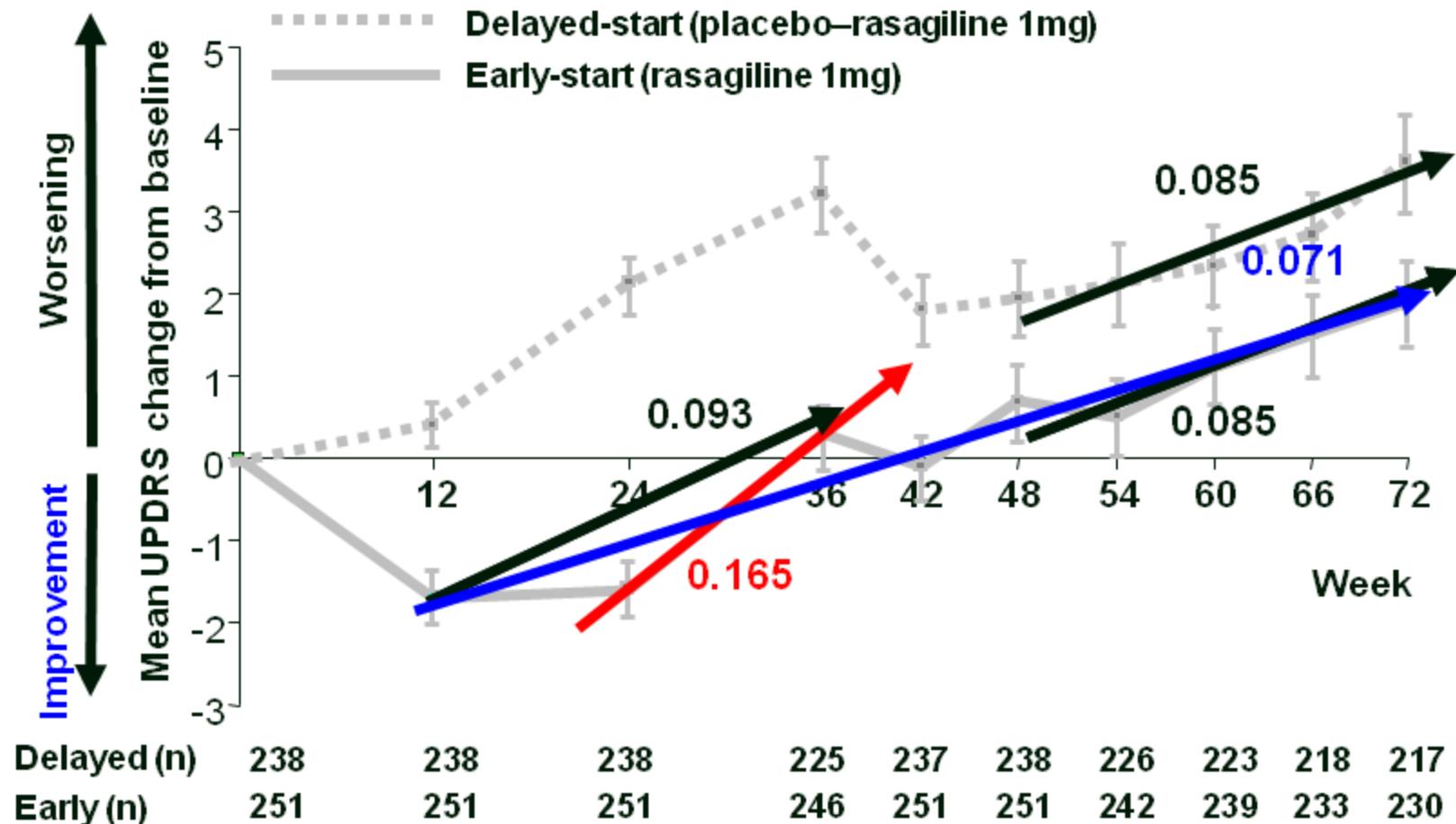
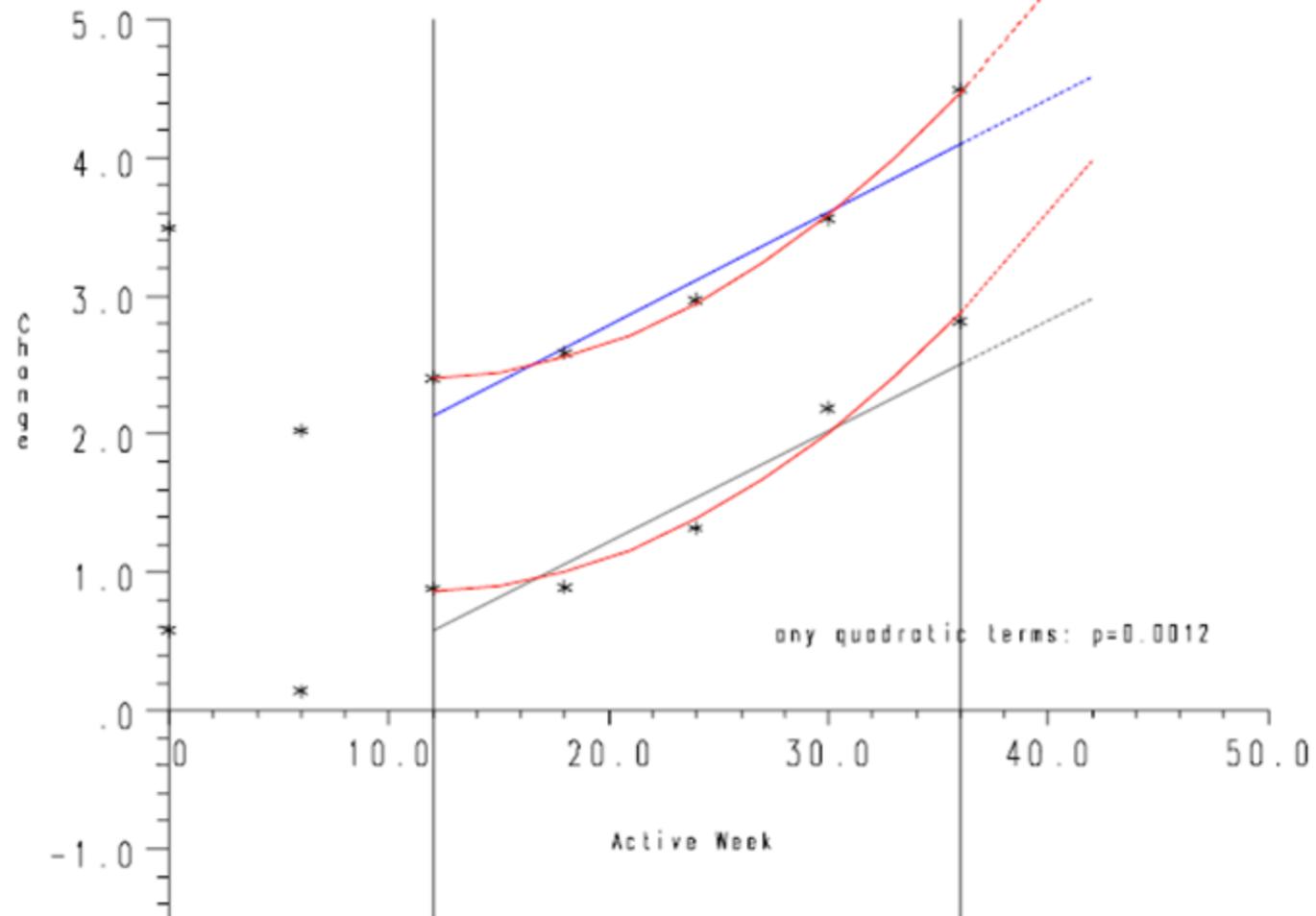
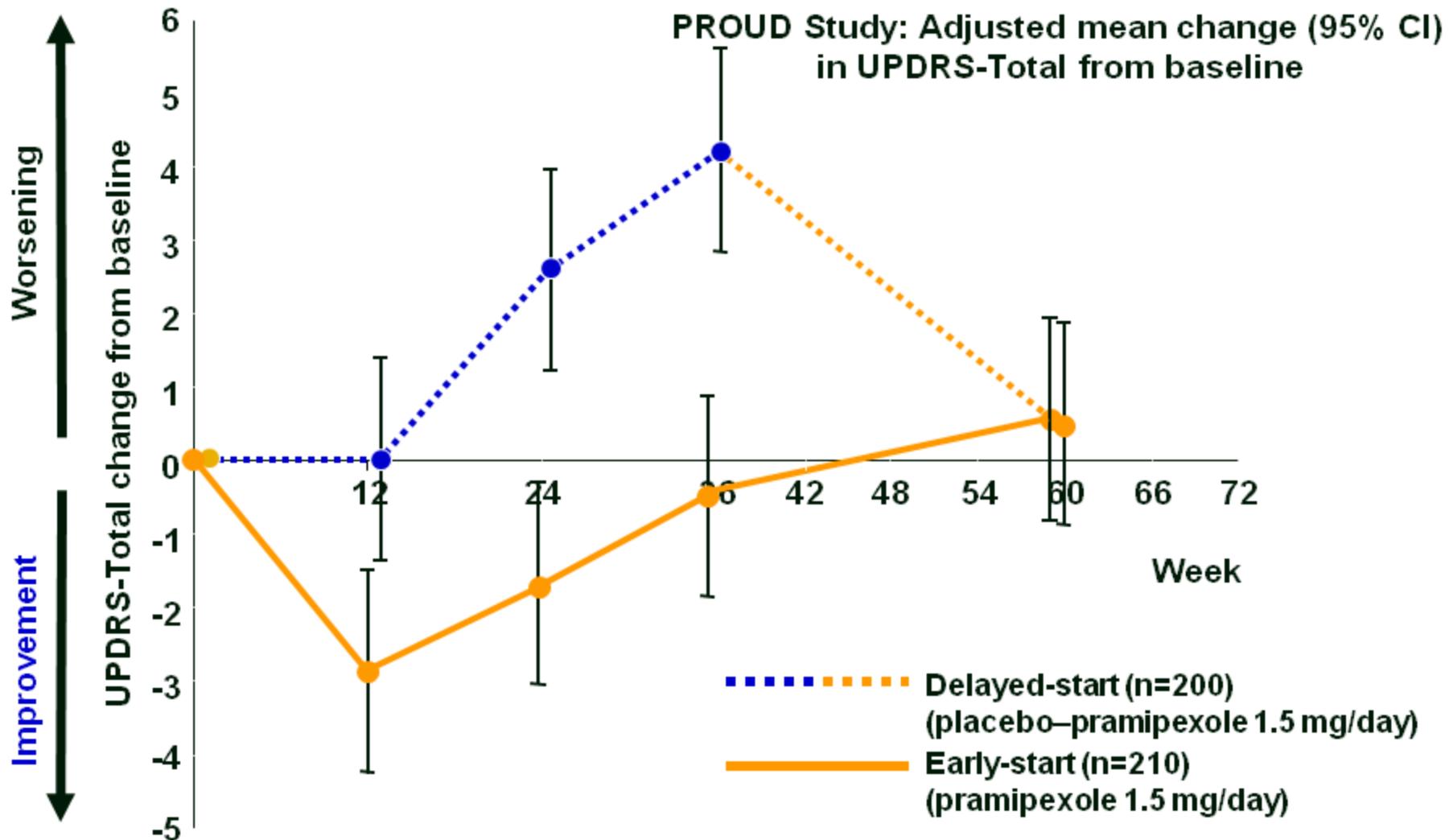


Figure 7 Change from Baseline in UPDRS during Active Phase (ACTE) for 1MG

ADAGIO: UPDRS for 1 mg in Active Phase
excluding active weeks 0 and 6 from analysis as per analysis plan



PROUD Results



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

ADAGIO PC Phase	Placebo	Rasagiline	Rasagiline
	(N=593)	1 mg	2 mg
	%	%	%
Fatigue	2.9	5.9	3.4
Constipation	3.2	4.9	2.4
Arthralgia	4.0	3.8	4.4
Dizziness	3.2	3.5	4.1
Fall	3.9	3.1	4.8
Musculoskeletal Pain	3.4	2.1	4.4