EMA EFPIA workshop
Break-out session no. 4

V2- Sept 19

Case Study Title: Mixed Effect Models for Trials of Disease Modifying Treatments

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BOS4 : Position statement and associated questions

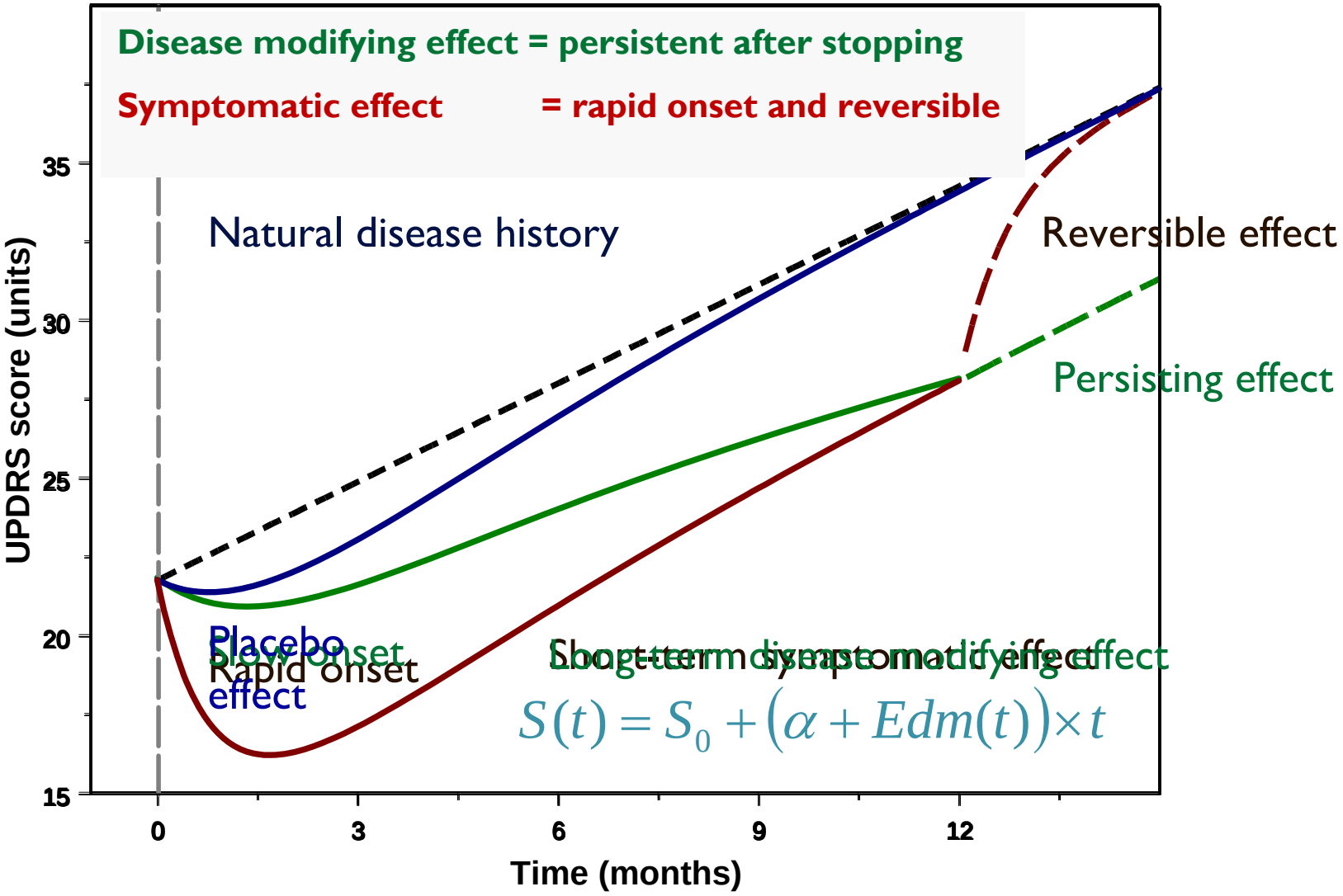
Position statement:

- "A parametric NLME approach offers a useful framework to design and analyse confirmatory trials that assess the impact of a new treatment on disease progression"

Questions:

- What is required to build greater acceptance of NLME approaches to analysis of disease progression trials within a regulatory environment?
- What would be required for an NLME approach to become a key secondary or primary analysis for assessing disease progression?

Treatment Effects in Parkinson's Disease



Background & Rationale I

A treatment effect in progressive diseases can be concluded based on a traditional analysis by contrasting the treatment and control arm at a single time point.

For progressive diseases it is valuable to know whether a drug effects alters the underlying progression rate of the disease (disease modifying effect) or produces a transient effect that will disappear after treatment is ceased (symptomatic drug effect)

To determine whether the drug treatment slows down the disease progression, an analysis using a single time point will not suffice, but requires a longitudinal analysis which NLME can provide.

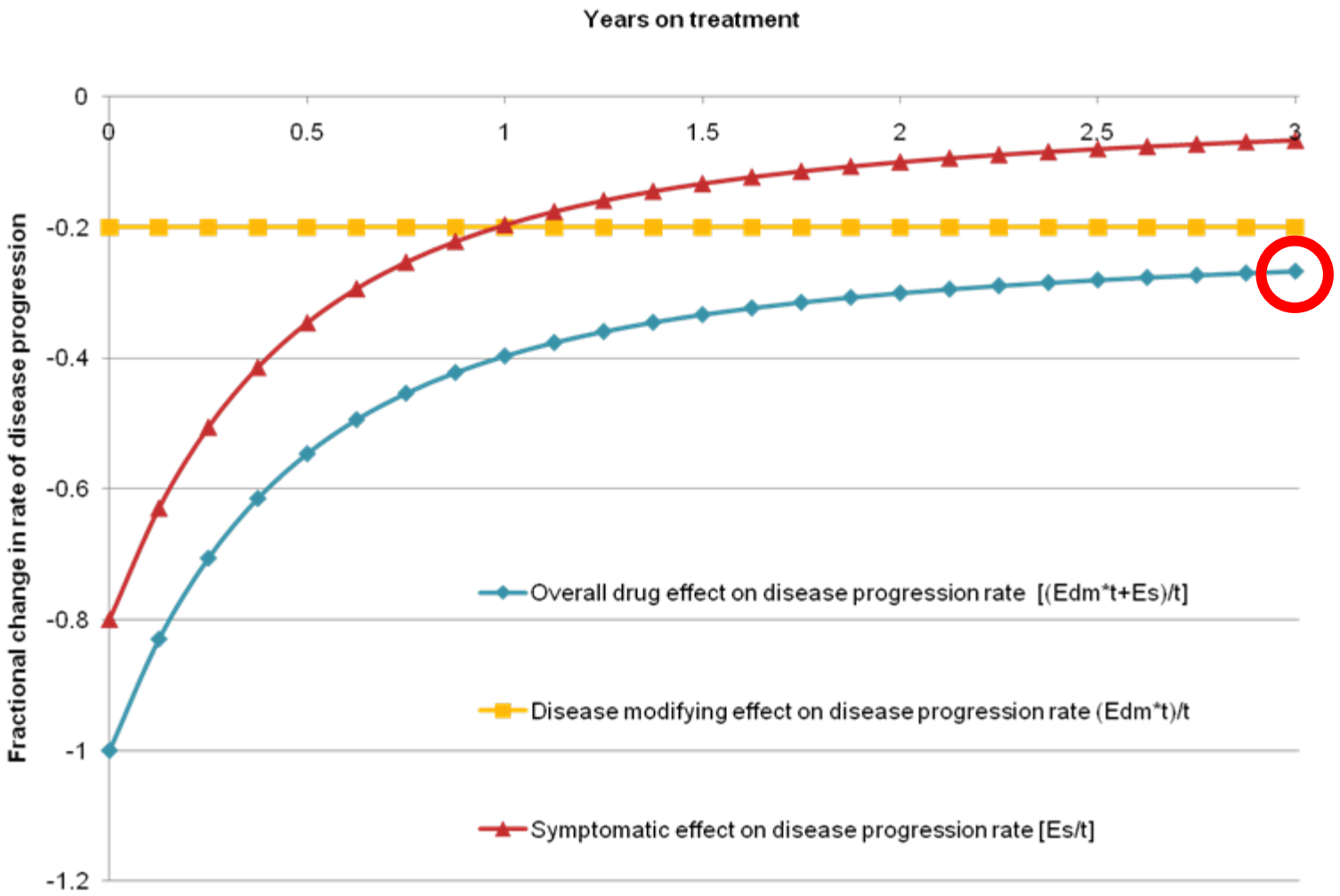
Objectives of the M&S work

- To determine the whether the drug treatment slows down the disease progression

Methods - estimation

- NLME includes longitudinal data, the entire time-course of responses for both arms, in the analysis.
- Structural aspects of the model are defined, together with interindividual parameter variability and residual error
- NLME estimates the disease progression/placebo effect and symptomatic and disease-modifying effects as explicit linear or non-linear models with time.
- The NLME model is most conveniently implemented as a differential equation to allow changes in rate of progression over time

Methods - simulation



Conclusions

Determination whether a treatment slows disease progression require utilisation of data from more than one point in time.

A NLME framework for performing a longitudinal analysis is the most successful approach to date for characterising treatment effects in Parkinson's Disease and may be turned into a model-based decision framework.

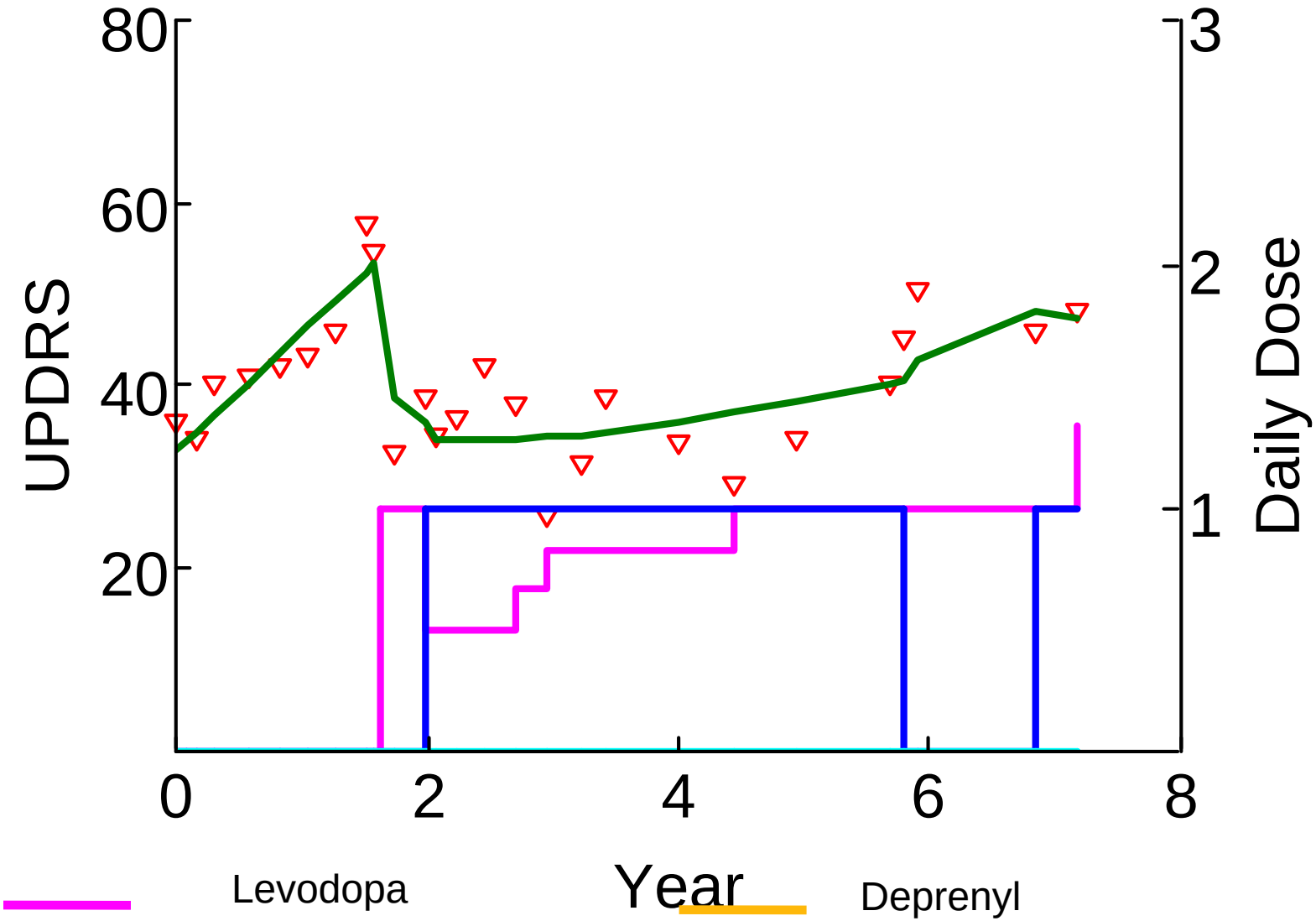
Subsequent data generated

- None

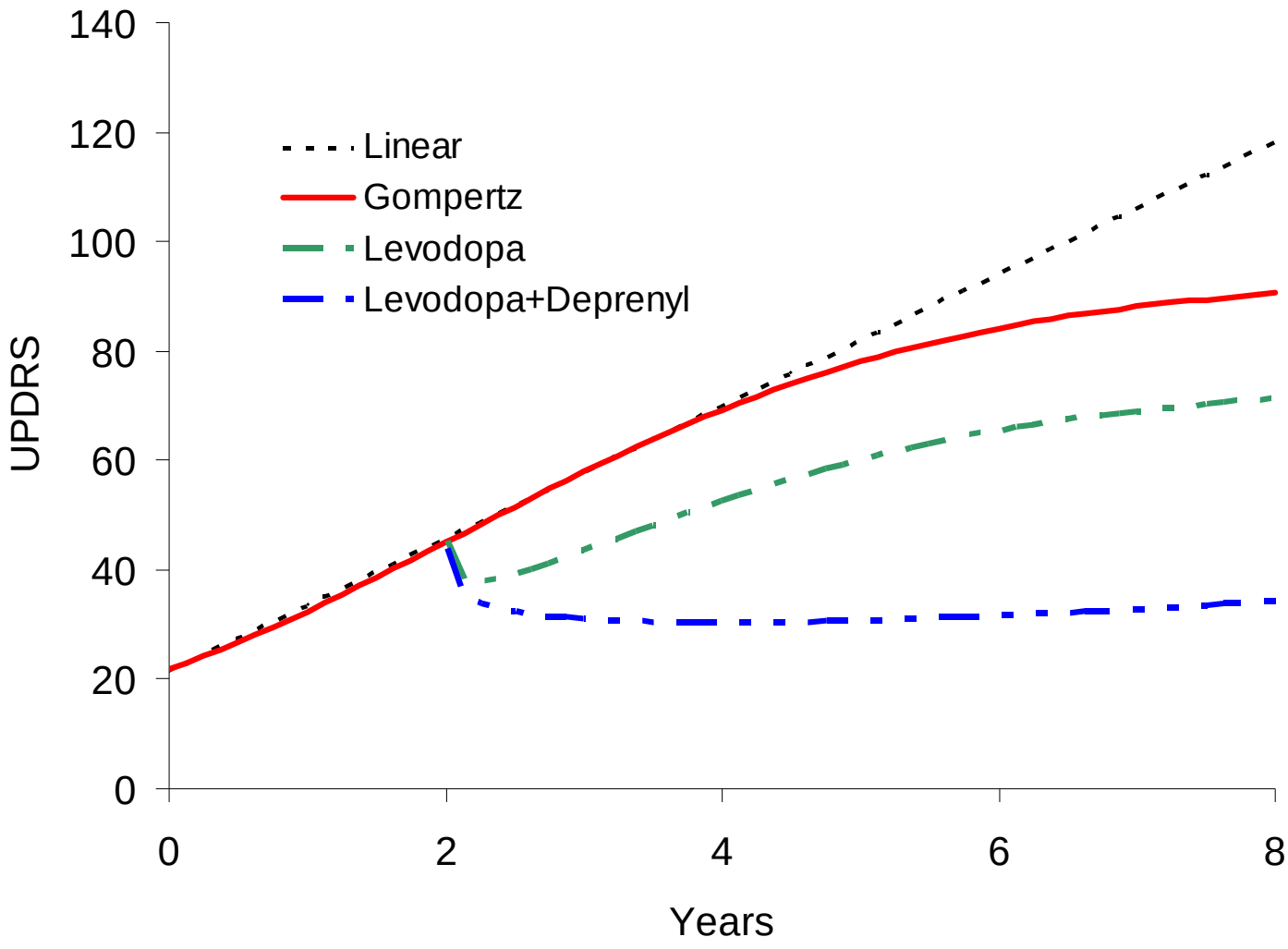
BOS4 : Additional slides

- The following slides are illustrations of some previous models and studies done in the field of Parkinson's Disease.

Offset + Slope Effect?



Symptomatic and Disease Modifying Effects



Three Strikes and You Are Out!

Didn't study disease

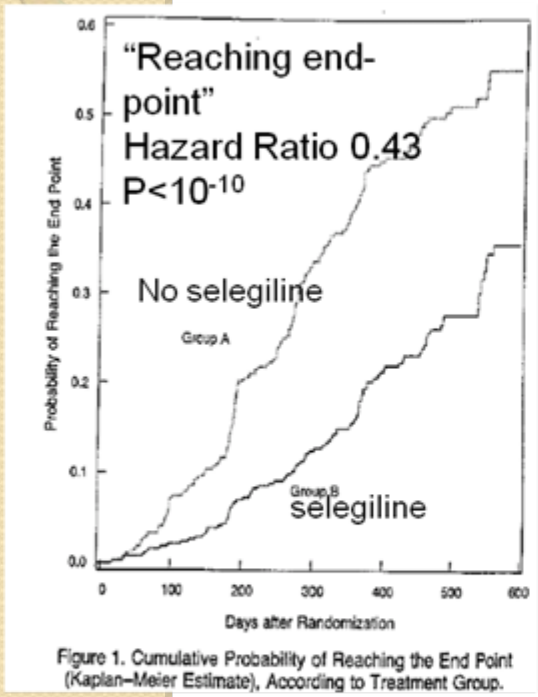
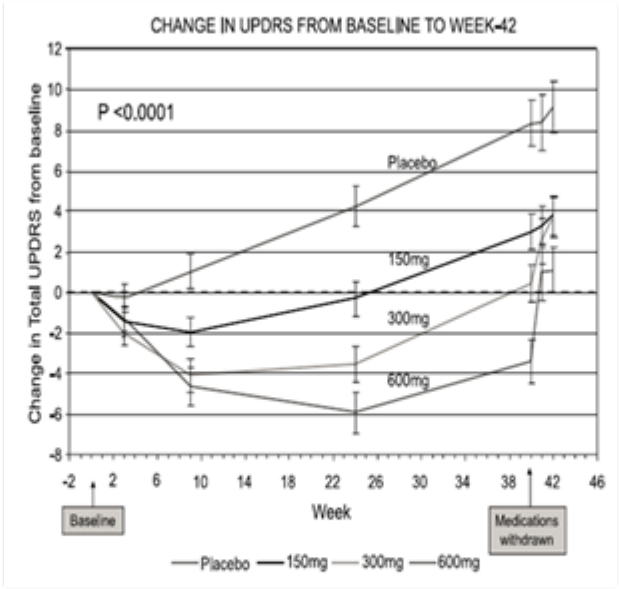


Figure 1. Cumulative Probability of Reaching the End Point (Kaplan–Meier Estimate), According to Treatment Group.

DATATOP
PSG 1989

No conclusion



ELLDOPA
Fahn 2006

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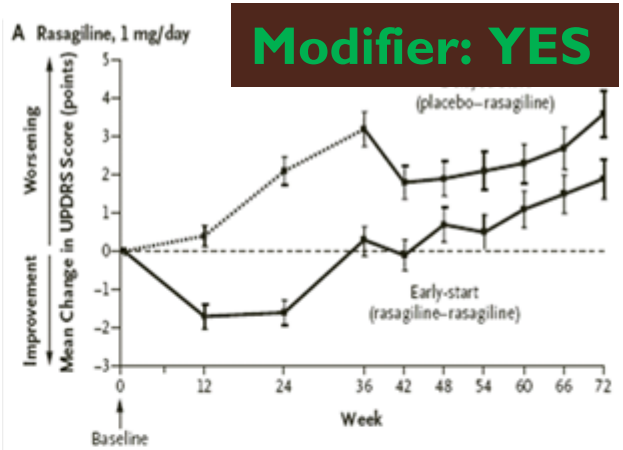

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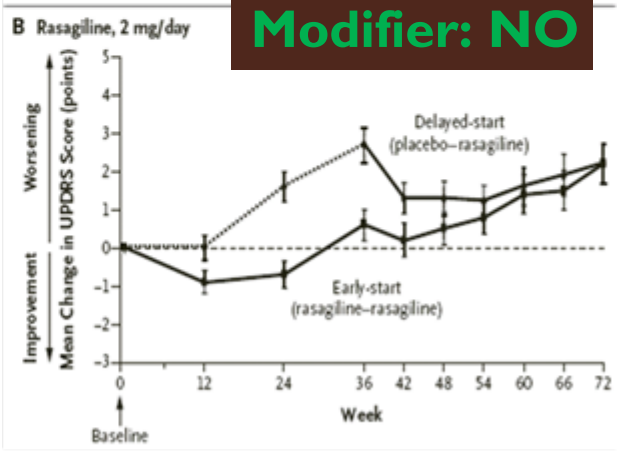
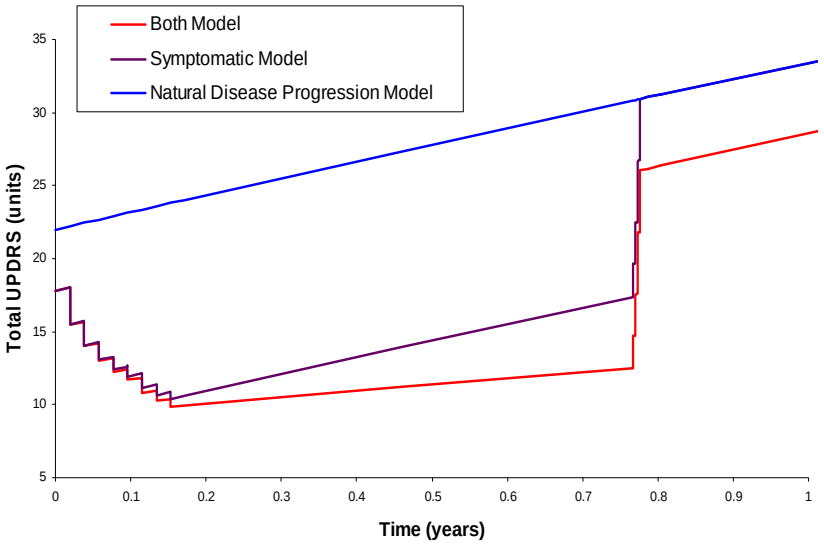
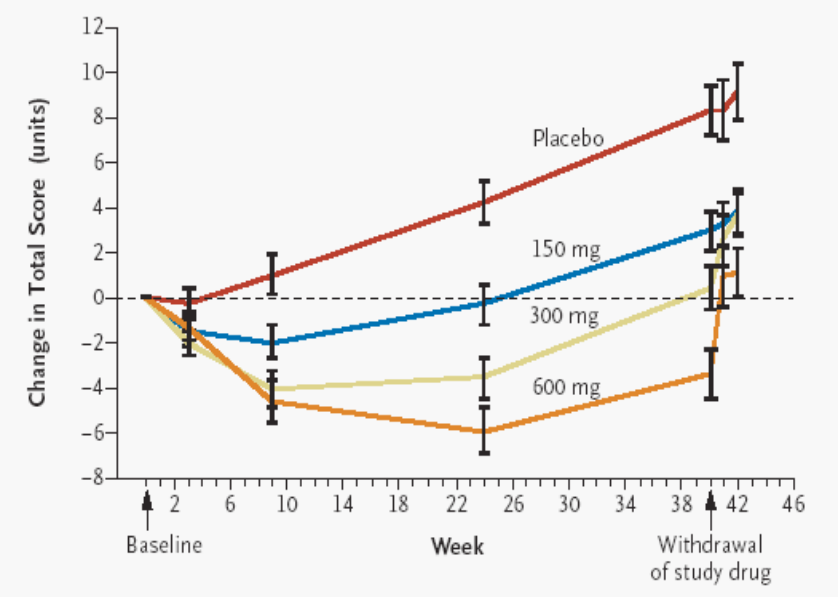


ADAGIO
Olanow et al 2009

ELLDOPA
Before and After



Design



Results

The Parkinson Study Group. Levodopa and the Progression of Parkinson's Disease. N Engl J Med 2004;351(24):2498-2508

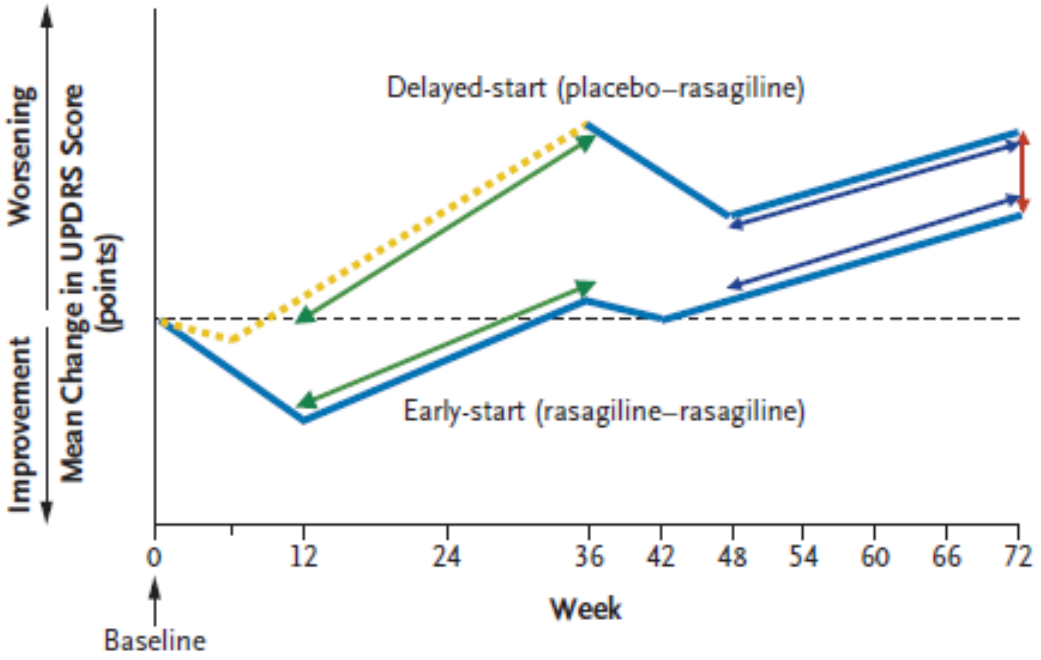


Figure 1. Schematic Illustration of the Three Primary End Points of the Study.

The three primary end points, which had to be met in a hierarchical fashion to declare positive results, are shown. The green arrows indicate the first end point: the superiority of early-start treatment versus placebo with respect to the estimate of the rate of change from baseline in the total Unified Parkinson's Disease Rating Scale (UPDRS) score between weeks 12 and 36. The red arrow indicates the second end point: the superiority of early-start treatment versus delayed-start treatment with respect to the estimate of change in the total UPDRS score between baseline and week 72. The blue arrows indicate the third end point: the noninferiority of early-start treatment as compared with delayed-start treatment with respect to the estimated rate of change from baseline in the slope for the total UPDRS score between weeks 48 and 72. The dashed yellow line indicates placebo, and the solid blue lines indicate rasagiline.

NEJM 361:13 (2009)