Trial Design, Endpoints for Disease Modifying Drugs in Parkinson’s Disease

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The views expressed in this presentation do not necessarily reflect the agency position
Why Alternate Designs?
Endpoints used for approving symptomatic drugs may not be applicable for disease-modifying claims

- Drugs to slow the progression of diseases such as Parkinson’s, Alzheimer’s are under development

- The importance of approving a drug for a disease-modifying claim, from a public health point of view, is paramount
  - An approval will potentially lead to switching a majority of patients currently on symptomatic treatments to disease-modifying treatment

- FDA is asked to comment on the acceptability of alternate trial designs and pre-specified analyses
  - Proactive effort by the agency to understand disease/baseline characteristics, disease progression, placebo/drug effects, and statistical issues (Missing data, etc)
  - Build upon early work by several experts
Key Regulatory Challenges

No experience in regulatory approval of disease-modifying drugs for Parkinson’s disease

- How do we describe the progression of Parkinson’s disease (Linear/Nonlinear)?

- What is the impact of missing data on hypothesis testing for disease-modifying claims?
Linear Model for Natural Disease Progression

Literature evidence and modeling at FDA using 1500 patient database

Literature Based Evidence

Mean (SD) of Total UPDRS scores for patients treated with Levodopa alone or in combination with Selegiline for 5 years and during the one-month washout period

Data Based Evidence

- Natural disease progression model with assumption of linear shape fits the data well
- Linear mixed effects analysis post a baseline visit (e.g., 12 weeks) can be used for slope based calculations
- Nonlinear mixed effects analysis using all the data can also be used for estimating slope. Linear mixed effects is numerically more stable
Drop-outs are Driven by the Need for Rescue Therapy
Understanding why patients discontinue in trials

- **Literature Based Evidence**
  - Predominant reason for drop-out of treatment (placebo or drug) is need for additional symptomatic therapy
  - Patients who need rescue therapy have worse symptoms (higher changes in UPDRS scores)

- **Data Based Evidence**
  - Graphical displays were generated to understand the drop-out pattern
    - Patients who discontinue early have higher change in clinical scores compared to patients who do not discontinue
  - Modeling patient drop-out
    - Parametric hazard model fits the data well
The Delayed Start Design
For a drug with a combined disease modifying and symptomatic effects

\[
\Delta \text{Score}_t = (\alpha \cdot Plc + \beta_P \cdot \text{Trt}) \cdot \text{Time} + (\beta_{Pc} \cdot Plc + \beta_S \cdot \text{Trt}) \cdot (1 - e^{k_e \cdot \text{Time}})
\]

- The UPDRS score was recorded at weeks 0, 4, 12, 24, 36, 42, 48, 54, 60, 66 and 72.
- Two phases
  - Placebo control phase (0-36 weeks) and active control phase (37-72 weeks).
Analysis of Placebo and Active Control Phases
Sequence of hypothesis tests at $\alpha=0.05$ in the simulation study

$1$ MEM- Mixed Effects Model
Analysis of Placebo and Active Control Phases

Sequence of hypothesis tests at $\alpha=0.05$ in the simulation study

- LSM - Least square means
- MMRM - Mixed Model Repeated Measures

$H_0: \text{LSM}_{\text{Early}} - \text{LSM}_{\text{Delayed}} = 0$

and Parallel slopes using MEM

$H_0: \text{SLOPE}_{\text{Early}} - \text{SLOPE}_{\text{Delayed}} > \delta$

$^2$LSM- Least square means; MMRM-Mixed Model Repeated Measures

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Delayed Start Design
Missing Data Assumptions
The disease progression, drug effect, and missing data models were employed to simulate 1000 replicates of the clinical trial per scenario

- **Missing Data Scenario**
  - Drop-out due to need for rescue therapy; Missing at Random (MAR)
    - Equal drop-outs
    - Unequal drop-outs
      - 45% vs. 35% due to symptom worsening
      - 45% vs. 30% due to drug toxicity

- **Drug Effect Scenario**
  - Treatment has no effect on slope of disease progression; a symptomatic drug (Type-1 Error)
  - Treatment has (15, 30, 50%) effect on slope of disease progression; a disease modifying drug (Power)
Type-1 Error
The proposed analysis sequence conserves Type-1 error

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Placebo Control</th>
<th>Active Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type-1 Error</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Equal Drop-outs</strong></td>
<td>6.3(0.006)</td>
<td>4.5(0.04)</td>
</tr>
<tr>
<td><strong>Unequal Drop-outs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>—Lack of Effectiveness</td>
<td>6.0(0.006)</td>
<td>≈0(-1.8)</td>
</tr>
<tr>
<td>—Toxicity</td>
<td>6.0(0.006)</td>
<td>4.7(0.28)</td>
</tr>
</tbody>
</table>

**Table:** Type-1 Error (Bias- Slope(Placebo control) and LSM(Active control) ) for MAR drop outs.
The proposed analysis sequence is also powerful.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Number of subjects for $\geq 80%$ power</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Power</strong></td>
<td>@50% effect on disease progression</td>
</tr>
<tr>
<td><strong>Equal Drop-outs</strong></td>
<td>200</td>
</tr>
<tr>
<td><strong>Unequal Drop-outs</strong></td>
<td></td>
</tr>
<tr>
<td>—Lack of Effectiveness</td>
<td>400</td>
</tr>
<tr>
<td>—Toxicity</td>
<td>400</td>
</tr>
</tbody>
</table>

When the drug effect was 15%, more than 700 patients were needed for 80% power for both scenarios.
Key Findings

The current knowledge and systematic evaluation of prior Parkinson’s trial database suggests that

- A slope based analysis on the placebo-control phase along with analysis of the active-control phase collectively should provide an acceptable statistical evidence of disease modifying effects.

- The proposed analysis sequence is powerful and conserves Type-1 error.

- Other trial designs and endpoints can also be explored with similar rigorous evaluation.
# Acknowledgments

## Internal and External Experts

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- Robert Temple MD, Office of New Drugs, Division of Neuropharmacological Drug Products
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- Jordan Elm MS, Medical University of South Carolina

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- Ramana Uppoor PhD, Office of Clinical Pharmacology
- Pharmacometrics Group, Office of Clinical Pharmacology

### Others
- Arthur Watts BS, University of Rochester
2008 AAPS Workshop

Demonstrating Disease-modifying Effects for the Treatment of Parkinson's Disease: Drug Development and Regulatory Issues

April 28-29, 2008
Hyatt Regency Crystal City
Arlington, VA

Get full program details and registration information at www.aapspharmaceutica.com/parkinsons

Co-sponsored with

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Delayed Start Design
### Typical Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope of disease progression in placebo group ($\beta_1$)</td>
<td>0.21 Units/Week</td>
</tr>
<tr>
<td>Slope of disease progression in treatment group ($\beta_2$)</td>
<td>0.13 Units/Week</td>
</tr>
<tr>
<td>Symptomatic effect in placebo group ($\beta_3$)</td>
<td>2 Units</td>
</tr>
<tr>
<td>Symptomatic effect in treatment group ($\beta_4$)</td>
<td>3 Units</td>
</tr>
<tr>
<td>Rate at which maximum symptomatic effect is achieved (in placebo and treatment group) ($k_{e0}$)</td>
<td>0.44 week^{-1}</td>
</tr>
</tbody>
</table>

### Interindividual Variability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Slope, (SD, %CV)</td>
<td>0.18; 85%</td>
</tr>
<tr>
<td>Symptomatic Effect, (SD, %CV)</td>
<td>4.55; 225%</td>
</tr>
<tr>
<td>Rate at which maximum symptomatic effect is achieved, (SD, %CV)</td>
<td>2.08; 208%</td>
</tr>
</tbody>
</table>

### Residual Variability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of model parameters used to simulate the longitudinal course of Parkinson's disease</td>
<td>2.84 Units</td>
</tr>
</tbody>
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