Clinical trial measures to capture important motor and non-motor outcomes in PD

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Disclosures

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Consulting

Legal Consulting
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Company Leadership  Clintrex (partner), Hoover Brown (principal)
Parkinson's Disease

• Progressive neurodegenerative disease
• Neuropathological diagnosis based on dipigmentation and cell loss from substantia nigra pars compacta
  – Lewy bodies in numerous brain regions
• Diagnosis made on clinical observation
PD Signs and Symptoms

**Motor**
- Akinesia, rigidity, and tremor at rest (asymmetric onset in general)
- Postural stability and gait impairment

**Non-Motor**
- Autonomic symptoms, cognitive impairment, pain, fatigue, olfactory dysfunction and psychiatric features (depression, hallucination)
Premotor/Prodromal
- Impaired olfaction
- Constipation
- Depression
- Excessive Daytime Sleepiness
- Rapid Eye Movement Sleep Behavior Disorder

Symptomatic
- Emergence and worsening of motor features (initiation of symptomatic treatment)
- Treatment-resistant motor and non-motor features with advancing disease
Effects of Tocopherol and Deprenyl on the Progression of Disability in Early Parkinson’s Disease
### UPDRS Composite Scale

<table>
<thead>
<tr>
<th>Part I</th>
<th>Non-motor aspects of experience of daily living</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mentation, behavior, mood</td>
</tr>
<tr>
<td>Part II</td>
<td>Motor aspects of daily living</td>
</tr>
<tr>
<td></td>
<td>Speech, swallowing, walking, etc.</td>
</tr>
<tr>
<td>Part III</td>
<td>Motor examination</td>
</tr>
<tr>
<td></td>
<td>Finger tapping – right &amp; left hands</td>
</tr>
<tr>
<td>Part IV</td>
<td>Complications of therapy</td>
</tr>
<tr>
<td></td>
<td>Functional impact of dyskinesia – yes/no</td>
</tr>
</tbody>
</table>

Parts I – III consist of 44 questions ranking from 0 to 4
Higher total score indicates more severe disease status
Levodopa and the Progression of Parkinson’s Disease

Changes in total UPDRS from baseline through evaluation at Week 42

Parkinson Study Group

Figure 2: MDS-UPDRS part 3 scores (A) and changes in MDS-UPDRS part 3 scores (B), by study visit
Data are means for the off-medication state. Error bars represent standard error of the mean
MDS-UPDRS=Movement Disorders Society Unified Parkinson’s Disease Rating Scale.
Mean (SE) total (parts I + II + III), motor, activities of daily living, and mental Unified Parkinson’s Disease Rating Scale scores during the course of the trial by treatment assignment.

Figure Legend:
Premotor/Prodromal
- Impaired olfaction
- Constipation
- Depression
- Excessive Daytime Sleepiness
- Rapid Eye Movement Sleep Behavior Disorder

Symptomatic
- Emergence and worsening of motor features (initiation of symptomatic treatment)
- Treatment-resistant motor and non-motor features with advancing disease
Pramipexole vs. Levodopa as Initial Treatment for Parkinson Disease. A randomized Controlled Trial

*first dopaminergic complication*  
*wearin-off*  
*dykinesias*

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PSG JAMA 2000; 284:1931-1938
NET-PD Long-Term Study 1 (LS1)
Design Considerations

The study is designed to assess whether creatine slows PD clinical decline.
Primary Measures of Clinical Decline & Dimensions Measured

1. Symbol Digit Modalities (verbal)
   - Cognitive Function

2. Schwab and England
   - Disability

3. PDQ-39 summary score
   - Quality of life

4. Sum of 5 UPDRS questions:
   Falling, Freezing, Walking, Gait, Postural Stability
   - Ambulatory Capacity

5. Modified Rankin Scale
   - Overall Clinical Assessment
### Table 2. Components of the Global Statistical Test by Treatment Group for LS-1 Cohort 1; Change From Baseline to Year 5<sup>a</sup>

<table>
<thead>
<tr>
<th>Components Included in the Computation of Global Outcome</th>
<th>Treatment Group, Mean (SD)</th>
<th>Difference, Mean (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory capacity score</td>
<td>Placebo (n = 478)</td>
<td>2.8 (5.0)</td>
</tr>
<tr>
<td></td>
<td>Creatine (n = 477)</td>
<td>3.1 (5.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−0.3 (−1.0 to 0.4)</td>
</tr>
<tr>
<td>Modified Rankin&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Placebo (n = 478)</td>
<td>2.1 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Creatine (n = 477)</td>
<td>2.2 (1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−0.1 (−0.3 to 0.1)</td>
</tr>
<tr>
<td>PDQ-39 Summary Index</td>
<td>Placebo (n = 478)</td>
<td>13 (23.2)</td>
</tr>
<tr>
<td></td>
<td>Creatine (n = 477)</td>
<td>14.2 (23.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−1.2 (−4.2 to 1.7)</td>
</tr>
<tr>
<td>Schwab and England ADL&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Placebo (n = 478)</td>
<td>14.8 (26.0)</td>
</tr>
<tr>
<td></td>
<td>Creatine (n = 477)</td>
<td>16.8 (28.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.0 (−5.5 to 1.5)</td>
</tr>
<tr>
<td>Symbol Digit Modalities&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Placebo (n = 478)</td>
<td>4.5 (16.8)</td>
</tr>
<tr>
<td></td>
<td>Creatine (n = 477)</td>
<td>4.9 (17.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−0.4 (−2.7 to 1.8)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADL, activities of daily living; LS-1, Long-term Study 1; PDQ-39, 39-Item Parkinson’s Disease Questionnaire.

<sup>a</sup> Cohort 1 includes those participants (n = 955) eligible for a 5-year follow-up visit at the time of interim analysis (July 17, 2013). Missing values are imputed.

<sup>b</sup> Placebo-treatment as reference group.

<sup>c</sup> Modified Rankin is the actual score at 5 years. All others outcomes are change from baseline to 5 years.

<sup>d</sup> Reverse coded such that higher scores indicate worse outcomes. Higher raw values are worse for all outcomes.
## Table 3. Secondary Outcome Measures for Cohort 1

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo No.</th>
<th>Placebo Mean (SD)</th>
<th>Creatine No.</th>
<th>Creatine Mean (SD)</th>
<th>Difference, Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total LEDD, (mean at year 5), mg</td>
<td>365</td>
<td>762 (408)</td>
<td>366</td>
<td>738 (401)</td>
<td>45 (-14 to 103)</td>
</tr>
<tr>
<td>UPDRS (mean change)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>336</td>
<td>10.4 (13.8)</td>
<td>330</td>
<td>11.3 (15.3)</td>
<td>-0.9 (-3.1 to 1.3)</td>
</tr>
<tr>
<td>Mental</td>
<td>339</td>
<td>1.1 (1.8)</td>
<td>333</td>
<td>1.2 (1.9)</td>
<td>-0.1 (-0.4 to 0.1)</td>
</tr>
<tr>
<td>ADL</td>
<td>339</td>
<td>4.0 (5.1)</td>
<td>333</td>
<td>4.5 (5.7)</td>
<td>-0.5 (-1.3 to 0.3)</td>
</tr>
<tr>
<td>Motor</td>
<td>336</td>
<td>5.3 (9.8)</td>
<td>330</td>
<td>5.6 (10.2)</td>
<td>-0.2 (-1.8 to 1.3)</td>
</tr>
<tr>
<td>Total functional capacity (mean change)</td>
<td>343</td>
<td>-1.7 (2.4)</td>
<td>334</td>
<td>-1.9 (2.7)</td>
<td>0.2 (-0.2 to 0.6)</td>
</tr>
<tr>
<td>Scales for Outcomes in Parkinson disease-Cognition (mean change)</td>
<td>315</td>
<td>-2.0 (4.9)</td>
<td>309</td>
<td>-1.9 (5.4)</td>
<td>-0.1 (-0.9 to 0.7)</td>
</tr>
<tr>
<td>EQ-SD (mean change)</td>
<td>342</td>
<td>-0.1 (0.2)</td>
<td>334</td>
<td>-0.1 (0.2)</td>
<td>0.005 (-0.03 to 0.04)</td>
</tr>
<tr>
<td>BDI score (mean at year 5)</td>
<td>335</td>
<td>8.5 (6.7)</td>
<td>329</td>
<td>8.6 (6.3)</td>
<td>-0.1 (-1.1 to 0.9)</td>
</tr>
<tr>
<td>BDI score &gt;17 (at year 5), No. (%)</td>
<td>335</td>
<td>29 (8.7%)</td>
<td>329</td>
<td>29 (8.8%)</td>
<td>0.002 (-0.04 to 0.04)</td>
</tr>
<tr>
<td>BMI, mean change</td>
<td>341</td>
<td>-0.4 (3.3)</td>
<td>338</td>
<td>-0.1 (2.9)</td>
<td>-0.3 (-0.8 to 0.2)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADL, activities of daily living; BDI, Beck Depression Inventory; BMI, body mass index; EQ-SD, EuroQOL instrument; LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson Disease Rating scale.

- **Data reported from final interim analysis (July 17, 2018) with the exception of BMI and total LEDD, which are reported from the final locked database (May 5, 2014).**

- **Values are means at year 5; BDI score greater than 17 is the difference in proportions at year 5.**

- **Values are mean change from baseline to year 5.**

- **Calculated as weight in kilograms divided by height in meters squared.**
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*
Next Steps

• PD is more than a motor disease - trials also need to address non-motor features
• Long-term disability and reduced health-related quality of life are valid endpoints
• Short-term trials will not reliably inform about a change in disease course
• Long-term trials need to have mechanisms to end early to avoid inefficiency