Characterizing Disease Progression for Parkinson’s Disease to implement efficient trial designs

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**Introduction**

A quantitative assessment of the patient characteristics and enrichment of clinical trials evaluating disease-modifying therapies for neurodegenerative disorders are critical to improve trial efficiency. CPP is pursuing regulatory qualification of prognostic enrichment biomarkers and characterize disease progression in early stage Parkinson’s Disease (PD) to enable selection of the most appropriate patient population for evaluating new therapeutic strategies in long-term clinical trials.

**Objectives**

The present work to develop a disease progression model and identify relevant patient characteristics to inform trial design for Phase 2/3 trials that evaluate therapeutic candidates for early stage PD.

**Methods**

C-Path assembled subject-level longitudinal data from 410 subjects with early-stage PD and dopamine transporter deficit from the PPmI study was used to build the disease progression model. Beta regression analyses, an extension of the generalized linear model, was used to characterize the time course of MDS-UPDRS Part II plus III due to its ability to evaluate bounded scores[1].

\[
f(Score_{\alpha}, \beta) = \frac{\frac{\gamma}{\Gamma(\gamma)} + \frac{\beta}{\Gamma(\beta)}}{\gamma + \beta} \cdot \text{Score}_{\alpha}^{\gamma} \cdot (1 - \text{Score}_{\alpha})^{\beta}
\]

Where \(\Gamma(\alpha)\) is the gamma function, that will be implemented in NONMEM using Neme approximation[2], and \(\alpha\) and \(\beta\) are shape parameters and Score [3] belongs to \(0, 1\) defined as

\[
\text{Score}_{\alpha} = \frac{\text{Score}_{\text{min}} \cdot \text{Score}_{\text{max}}}{\text{max}(\text{Score}) - \text{min}(\text{Score})}
\]

\[
\text{Score}_{\beta} = \frac{\text{Score}_{\text{max}} - \text{Score}_{\text{min}}}{n - 1} + 0.5
\]

**Results**

Base model structure selection commenced with a linear model followed by non-linear models of increasing complexity [4].

**Table 1: Base Model development**

<table>
<thead>
<tr>
<th>Base models</th>
<th>Disease progression rate</th>
<th>OBFV</th>
<th>*BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear (normal distribution)</td>
<td>linear</td>
<td>1811.97</td>
<td>1815.43</td>
</tr>
<tr>
<td>linear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear (beta Distribution)</td>
<td>linear</td>
<td>-5930.941</td>
<td>-5890.684</td>
</tr>
<tr>
<td>exponential model</td>
<td>non-linear</td>
<td>-6703.357</td>
<td>-6664.901</td>
</tr>
<tr>
<td>Standard logistic model</td>
<td>non-linear, inflection point=57</td>
<td>-6719.668</td>
<td>-6787.21 (Final Base Model)</td>
</tr>
<tr>
<td>Generalized logistic model</td>
<td>non-linear, inflection point=49.4</td>
<td>-6718.797</td>
<td>-6720.249</td>
</tr>
</tbody>
</table>

**Conclusion**

A logistic model describing the disease progression in early stage PD was successfully developed. The insights from this model represent valuable information for building a more robust disease progression model that will inform the entry criteria and enrichment strategies for long-term trials.

- A logistic (non-linear) model was chosen based on goodness-of-fit plots and BIC criteria.
- The progression rate increased with time until the inflection point and the maximum progression rate was estimated to be ~0.25 points/month.
- Preliminary covariate analysis indicated that age had a significant effect on baseline, and gender and GBA mutation had a significant effect on the slope of disease progression.

**References**


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**Visual Predictive Check (VPC) from N = 1000 Simulations. Solid and dashed black lines are observed median, 5th and 95th percentiles, and shaded areas are corresponding predicted intervals from the final model. A) full dataset, B) stratified by GBA. Majority of the observations fall within the 95% prediction intervals suggesting the adequacy of the model to describe the individual temporal profiles.**

**Impact of selected covariates on disease progression**

The effect of statistically significant covariates was simulated using 1000 parameters, bootstrapping simulations. The reference/hyper-typical patient is a 62 year old male without GBA mutation. A) Effect of AGE on baseline, B) Effect of Gender on disease progression rate, C) Effect of GBA mutation on disease progression rate.