Background and Objectives

- One of the primary issues for Parkinson’s disease (PD) drug development is identifying patients at early stages prior to advanced neurodegeneration. As therapeutic trials aim at earlier stages of PD, appropriate patient selection based purely on clinical criteria is a significant challenge.
- The Critical Path for Parkinson’s (CPP) Consortium is a multinational coalition of scientists from industry, patient-advocacy groups, academia, and government. CPP aims to accelerate drug development with focus on early stages of Parkinson’s disease, a time when a process of opportunity to delay disease progression.

The goal is to exclude from PD clinical trials evidence of dopamine deficiency (SWEDDs), who are unlikely to progress in clinical trials of novel PD therapies. The team is advancing this project through formal drug development tool biomarker qualification review processes as per guidance documents.

Methods

- CPP’s PD imaging biomarker team seeks to qualify the use of DAT imaging biomarker to identify subjects with early motor dysfunction in clinical trials of novel PD therapies. The team is advancing this project through formal drug development tool biomarker qualification review processes as per guidance documents.

The proposed contribution of DAT neuroimaging is an enrichment biomarker for potential inclusion in a clinical trial of patients with a dopamine transporter (DAT) deficit who will be identified at the earliest signs of clinical motor impairment, when candidate therapeutic drugs pharmacologically can most effectively disrupt the progressive clinical motor decline of these patients. The team is advancing this project through formal drug development tool biomarker qualification review processes as per guidance documents.

Literature Review: A comprehensive literature review was conducted to identify observational and clinical studies that utilized DAT imaging per specifically defined inclusion and exclusion criteria. The inclusion of SWEDD cases in published reports of clinical trials of drugs that were discontinued was reviewed.

Figure 1 outlines the decision tree for the literature review.

Data sources: Observational cohort: PRIME, Realized Clinical Trial. Tessa previously provided a CoPath to the de-identified patient information data from PRECEPT, a large multicenter trial of the MAO-B inhibitor CEP1347 (Ref 5, 6).


Baseline PRECEPT results as % Age expected

Table 1 Results from longitudinal clinical trial (PRECEPT) showing difference in outcomes between SWEDD and non-SWEDD participants (Ref 4).

<table>
<thead>
<tr>
<th>SWEDD subjects show reduced rate of progression</th>
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<tbody>
<tr>
<td>DAT deficit</td>
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<tr>
<td>% Decrease</td>
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<td>----------------</td>
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<tr>
<td>% Decrease</td>
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<tr>
<td>Clinical</td>
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<td>Cognitive</td>
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<td>Quality of Life</td>
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<td>Mood</td>
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<td>Social</td>
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Table 1 Results from longitudinal clinical trial (PRECEPT) showing difference in outcomes between SWEDD and non-SWEDD participants (Ref 4).

SWEDDs showed minimal change in dopamine transporter deficit and in clinical progression at 16 months compared to dopaminergic deficit subjects from Ref 5.

Regulatory Implications

- "We encourage the use of this biomarker in clinical trials to enable its utility for the identification of subjects who do not progress and are unlikely to have idiopathic PD." SWEDDs and SWEDD- like subjects who do not progress and are unlikely to have idiopathic PD.

Both quantitative and visual assessment of DAT deficit provide comparable results.

- DAT deficiency assessed by SPECT imaging can help to enrich clinical trial populations with subjects more likely to show relevant disease progression, improve statistical power, and spare subjects who do not have PD from being exposed to novel therapeutic agents.

- Advantages of the consortium approach to achieving regulatory qualification include: sharing of costs and risks, sharing of precompetitive data, and consensus building on standardization and harmonization.

- The goal is to reduce the probability of success in future PD therapeutic trials.

Conclusions

- Data from the PRECEPT and PRIME studies demonstrate that baseline DAT imaging distinguishes PD patients from subjects who do not progress and are unlikely to have idiopathic PD.

- Both quantitative and visual assessment of DAT deficit provide comparable results.

- DAT deficiency assessed by SPECT imaging can help to enrich clinical trial populations with subjects more likely to show relevant disease progression, improve clinical research power, and spare subjects who do not have PD from being exposed to novel therapeutic agents.

- The goal is to reduce the probability of success in future PD therapeutic trials.

References


5. Ref 4


7. Ref 5


