Background

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 Institute's Critical Path for Parkinson's (CPP) Consortium is a multinational consortium of scientists from industry, patient advocate groups, academia, and government. CPP aims to accelerate drug development with focus on early stages of Parkinson's disease (PD), a time when there is promise of opportunity to delay disease progression. A key goal of CPP is to identify novel translational biomarkers and quantitative drug development platforms with regulatory agencies for use in early clinical trials to allow efficient development and validation of new therapeutic candidates (Ref 1).

Objectives

CPP's PD imaging biomarker team aims to achieve regulatory endorsement with FDA and EMA for the application of reduced dopamine transporter (DAT) density, measured by SPECT imaging, as a diagnostic biomarker for PD clinical trial enrichment. The target population is aimed at patients in early motor stages of Parkinson's disease soon after diagnosis when therapies hold promise for delaying progression.

Methods

CPP's PD imaging biomarker team seeks to qualify the use of DAT imaging biomarker to enrich subjects with early motor PD who are participating in clinical trials of novel PD therapies. The team is advancing this project through formal drug development tool biomarker qualification review programs as per guidance documents. The authors acknowledge the contributions of Dr. Maria Isaac (EMA) and Dr. Gerald Podskalny, FDA Liaison to CPP. CPP authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). Any views expressed in this publication represent the personal opinions of the authors, and not those of their respective employer. The authors' respective organization was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

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 rate of scans without evidence of dopamine deficit (SWEDD) cases in published reports of clinical trials to date was reviewed. Figure 1 outlines the decision tree for the decision tree.

Figure 1: Comprehensive literature review carried out to support Qualification of the Biomarker

Table 1: SWEDDs in PD Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Image- PD</th>
<th>Dev at 12 of Baseline (in.)</th>
<th>% SWEDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elloba</td>
<td>PRECEPT MKX</td>
<td>1.7 (186/104)</td>
<td>11.9</td>
</tr>
<tr>
<td>Elloba</td>
<td>PRECEPT REAL</td>
<td>1.5 (186/104)</td>
<td>12.1</td>
</tr>
<tr>
<td>DALDAQ</td>
<td>PRECEPT MKX</td>
<td>1.8 (186/104)</td>
<td>11.7</td>
</tr>
<tr>
<td>DALDAQ</td>
<td>PRECEPT REAL</td>
<td>1.7 (186/104)</td>
<td>12.0</td>
</tr>
<tr>
<td>Elloba</td>
<td>L-Dopa- PRECEPT MKX</td>
<td>1.8 (186/104)</td>
<td>11.9</td>
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<tr>
<td>Elloba</td>
<td>L-Dopa- PRECEPT REAL</td>
<td>1.7 (186/104)</td>
<td>12.1</td>
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Conclusion

Exclusion of SWEDD subjects in future clinical trials aims 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.

Regulatory science focus of the precompetitive consortium initiative CPP promises to increase the probability of success in future PD therapeutic trials aimed at tools to enable treatments in early stages of the disease.

References

(2) adultos. Diabetes Care; 2018; 41(12): 2375-2377.