DRUG DEVELOPMENT TOOL
LETTER OF SUPPORT
DDT-BMQ-000157

August 19, 2024

Critical Path Institute
Critical Path for Parkinson's
Attention: Diane Stephenson, PhD
Executive Director
1840 E. River Rd.
Tucson, AZ 85718

Dear Dr. Stephenson:

The FDA is issuing this Letter of Support to the Critical Path for Parkinson's consortium to encourage the further study and use of alpha-synuclein (α-syn) seed amplification assay (SAA) in human cerebral spinal fluid (CSF) samples to improve the efficiency of clinical trials targeting early intervention for neurodegenerative diseases defined by the common underlying biology, α-syn.

Research over the past decade has implicated brain accumulation of neuronal misfolded proteins as primary pathologic features of many neurodegenerative diseases, including Parkinson's disease (PD) and dementia with Lewy bodies (DLB). In some diseases, these proteins can be detected in vivo years before the onset of clinical symptoms and have the potential to be used to provide more consistent identification of underlying biology in the earliest stages of disease.

Alpha-synuclein seeding amplification assay is recommended to be used as a susceptibility / risk biomarker for enrichment of clinical trials of PD and related clinical syndromes with participants who are biologically defined as positive for the pathologic hallmark protein, synuclein. This group of neurodegenerative diseases is typically diagnosed by clinical symptomatology, but they share a common underlying biology based on the presence of pathologic α-syn, which can be assessed in vivo by α-syn SAA. Recently, a new biological definition and staging framework for diseases characterized by α-syn pathology was developed by a team of international experts and patient organizations. This framework, neuronal α-synuclein disease integrated staging system (NSD-ISS), proposes how biomarkers can be used in therapeutic development

for PD and related conditions.[1] This biologic definition is based on the presence of α-syn pathology, and is independent of the presence of clinical features, or if present, of the specific clinical syndrome.

The class of neurodegenerative diseases defined by the presence of α-syn encompasses what is conventionally referred to as PD, DLB, and related clinical syndromes. Clinical terminology includes:

- PD
- DLB
- Lewy Body Disease
- Lewy Body Dementia
- PD dementia
- Prodromal PD
- Prodromal DLB
- Rapid Eye Movement sleep behavior disorder

The traditional gold standard for identification of the pathogenic protein α-syn have relied on postmortem evaluation of α-syn by immunohistochemistry in autopsy tissue of patients clinically diagnosed with PD or DLB in life. Therefore, it has not been possible to reliably assess α-syn in living humans until very recently. The lack of biomarkers to detect α-syn in vivo has hindered clinical practice and clinical trials. People with lived experience communicate challenges with early and accurate diagnosis, and available treatments target motor symptoms with limited duration of efficacy. Such limitations have impacted therapeutic trials.

α-syn SAA is a technique that enables the detection of very small amounts of misfolded α-syn aggregates (α-syn seeds) in biosamples of human CSF with high sensitivity and specificity. SAAs represent ultrasensitive assays which exploit the seeding capacities of prion or prion-like proteins as an amplification strategy to reveal minute amounts of disease-specific protein aggregates in biosamples, including CSF. The α-syn SAAs produce consistently robust results in sensitivity and specificity in identifying patients with PD compared to healthy controls and other non-synuclein neurological disorders, and can be measured reliably in at-risk individuals several years prior to onset of clinical symptoms. Assessment of α-syn by SAA represents a methodology that may enable the

[1] T Simuni, LM Chahine, K Poston, et al. "A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research." Lancet Neurol 2024; 23: 178–90.

development of interventions for Parkinson's disease and biologically related conditions prior to onset of clinical manifestations.

Data in the Letter of Support document outlines the rationale for the role of α-syn in the pathophysiology of PD and related conditions, and highlights results of α-syn SAA in CSF from multiple independent observational cohorts in geographically diverse populations, as well as in two recent randomized controlled clinical trials of α-syn targeted therapeutic studies.

Strong emphasis on applying good scientific, laboratory, and software development practices for quality control and validation of misfolded α-syn as assessed by SAA in human CSF is imperative and timely. An initiative led by the Michael J. Fox Foundation (MJFF) has been underway to support the assay validation and implementation of α-syn SAA in CSF and other biosamples. Important supporting evidence came from MJFF's Parkinson's Progression Markers Initiative (PPMI) study, a global multi-stakeholder effort that included clinically diagnosed PD patients, healthy controls, and prodromal or non-manifesting carriers of genetic variants associated with PD. The study assessed changes in biomarkers at different stages of disease and evaluated whether SAA had the potential to detect PD in patients before the onset of motor symptoms. Key success factors for PPMI include the alignment, harmonization, and transparency of data collection methodologies and open sharing of data. New worldwide collaborative initiatives across disease areas will be important to expand evaluation of α-syn SAA in multiple cohorts. More experience with the use of this biomarker in research studies, including observational natural history studies and clinical trials, will be useful to determine its utility more accurately as a selection biomarker in clinical trials targeting neurodegenerative diseases characterized by neuronal α-syn.

We support Critical Path for Parkinson's consortium in issuing a Letter of Support for the application of binary assessment of α-syn SAA as an enrichment biomarker for patient selection in clinical trials investigating therapies that are intended to treat, prevent, or delay neurodegenerative disorders characterized by a common synuclein biology. The timing for this letter aligns with the growing number of disease-modifying candidates in development including innovative trial designs focused on prevention.

We encourage exploration of a-syn seeding assay measurement in human CSF as enrichment biomarkers for patient selection in clinical trials investigating therapies that are intended to treat or prevent neurodegenerative diseases characterized by neuronal α-syn. Sharing of patient-level data from clinical trials and natural history studies is encouraged to enable confidence in the use of this biomarker as a drug development tool according to the proposed context of use.

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Diane Stephenson, Executive Director, Critical Path for Parkinson's or view www.c-path.org.

Regards,

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