CRITICAL PATH INSTITUTE

FDA Issues ‘Letter of Support’ Encouraging Use of Synuclein-based Biomarker, ?Syn-SAA, in Clinical Trials in Parkinson’s and Related Diseases

- U.S. regulatory agency recognizes potential of alpha-synuclein seed amplification assay (?Syn-SAA) to accelerate clear outcomes in drugmakers’ trials
- Letter is latest milestone in the journey of the biomarker, discovered in 2023, to transform drug development focused on synuclein pathology — a biological hallmark of Parkinson’s, Dementia with Lewy Bodies and related neurodegenerative conditions
- FDA notes critical role of the Parkinson’s Progression Markers Initiative in generating and validating data and studies that made this landmark step forward possible

NEW YORK, NY AND TUCSON, AZ (September 9, 2024) — The U.S. Food and Drug Administration (FDA) encouraged scientists and drug developers to use the alpha-synuclein seed amplification assay (?Syn-SAA) biomarker, discovered in 2023, for research and clinical trials in a “Letter of Support” issued late Summer 2024. The Letter of Support follows multi-stakeholder collaboration amongst The Michael J. Fox Foundation for Parkinson’s Research (MJFF) and the Critical Path Institute (C-Path), with both organizations supporting use of the biomarker for clinical trials and advancing new drugs for Parkinson’s disease (PD). Because the tool can objectively detect early biology related to Parkinson’s and related diseases, including Dementia with Lewy Bodies (DLB), even before any symptoms emerge, trials using the biomarker are better positioned to test therapies that aim to delay or even prevent the onset of disease. The use of the tool also enables research toward tailored therapies to treat individuals at all stages of these diseases.

In the letter, FDA emphasizes that their support stems from significant evidence collected as part of MJFF’s flagship Parkinson’s Progression Markers Initiative (PPMI), which first **validated** the ?Syn-SAA biomarker in April 2023.

The assay detects early changes in synuclein, one of the two biological hallmarks of Parkinson’s disease. The other biological hallmark is dopaminergic transport dysfunction, which researchers have had the ability to visualize since the early 2010s using a brain imaging technology called DaTScan. The use of DAT Spect Imaging in clinical trials, also supported by MJFF and PPMI data, received similar FDA backing through a Letter of Support in March 2015 as led by C-Path’s Critical Path for Parkinson’s Consortium (CPP).

Earlier this year, a multistakeholder team including academic researchers and clinician scientists, industry, nonprofits, regulators, and people affected by Parkinson’s published the first biological staging system for Parkinson’s disease known as the neuronal alpha-synuclein disease integrated staging system (NSD-ISS), in ***The Lancet Neurology*****.** The staging system was made possible by the newfound ability to detect both biological hallmarks of the disease. The FDA Letter of Support recognizes the potential of NSD-ISS alongside data generated by ?Syn-SAA to accelerate the success of scientific discovery and therapeutic development.

“This FDA Letter of Support is a transformative moment for the field, promising to speed clinical trial design in Parkinson’s and related disorders,” said Diane Stephenson, PhD, executive director, CPP, C-Path. “The cross-collaboration among patients, researchers, clinicians, regulators and patient advocacy organizations demonstrates the critical role every player holds in moving today’s achievement forward. Now, we’re closer

than ever to better treatments, and perhaps one day, preventing people from developing the symptoms of these diseases altogether."

Biomarker Backed by Gold-Standard Parkinson's Study Will Accelerate Drug Development

The FDA's Letter of Support notes that data supporting ?Syn-SAA emerged largely from the Foundation's landmark PPMI study. This longitudinal observational study has built the most robust dataset and biosample library ever assembled in Parkinson's research, resources shared with the broader research community in real time for ongoing discovery and validation studies around the world. (Since the study's launch in 2010, PPMI data has been downloaded millions of times by researchers globally, on average more than 2,000 times a day.) Heralded as "the study that's changing everything" about how Parkinson's is diagnosed, managed and treated, PPMI and its data are made possible by more than 3,000 in-clinic and 42,000 online research volunteers with and without Parkinson's disease. The Letter of Support states: "Key success factors for PPMI include the alignment, harmonization, and transparency of data collection methodologies and open sharing of data."

Major funding for PPMI comes from Aligning Science Across Parkinson's (ASAP), a coordinated research initiative focused on accelerating the pace of discovery and informing the path to a cure for Parkinson's disease. ASAP support is enabling the seismic expansion of PPMI to increase recruitment efforts and remote testing for those at-risk for PD as well as expanding assay development efforts to enable breakthroughs such as ?Syn-SAA. This infrastructure provides a ready platform for future discoveries.

The Letter of Support, in addition, goes on to say that the decision to encourage use of ?Syn-SAA has also relied on other well-characterized global studies from across industry and academia, representing the wealth of evidence backing the tool, as well as the fieldwide collaboration used to validate it.

"The search for a Parkinson's biomarker has been a centerpiece of The Michael J. Fox Foundation's mission-critical work since our earliest days," said Todd Sherer, PhD, MJFF's chief mission officer. "As we continue working urgently toward better treatments and a cure, the FDA's backing of ?Syn-SAA is an important milestone in advancing today's robust pipeline of Parkinson's therapies that patients and families urgently need."

Clinical trials for potential new Parkinson's therapies are historically time-consuming and costly. From testing through approval, the development of a single new therapy takes decades and costs billions of dollars. As an objective and reliable biomarker of Parkinson's biology supported by the FDA, ?Syn-SAA holds potential to make these trials faster, clearer and more efficient, significantly decreasing the risk for industry to invest in the development of potential blockbuster therapies, including preventive agents. With ?Syn-SAA in hand, it will be possible to establish objective endpoints for clinical trials of Parkinson's treatments, ensure study participants exhibit relevant pathology, and detect therapy-induced changes in their status.

"In my conversations to my fellow patients, I have used the analogy of previous Parkinson's drug research as 'cave exploration in the dark'," said Kevin Kwok, PharmD, former biopharmaceutical executive, PPMI community advisory board member and patient advocate diagnosed with PD in 2009. "PPMI's biomarker initiative has resulted in the creation of an alpha-synuclein 'lantern' so we are no longer groping in the darkness but now have biological illumination of the cavern we are exploring."

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

About The Michael J. Fox Foundation for Parkinson's Research (MJFF)

As the world's largest nonprofit funder of Parkinson's research, The Michael J. Fox Foundation is dedicated to accelerating a cure for Parkinson's disease and improved therapies for those living with the condition today. The Foundation pursues its goals through an aggressively funded, highly targeted research program coupled with active global engagement of scientists, Parkinson's patients, business leaders, clinical trial participants, donors and volunteers. In addition to funding $2 billion in research to date, the Foundation has fundamentally altered the trajectory of progress toward a cure.?Operating at the hub of worldwide Parkinson's research, the Foundation forges groundbreaking collaborations with industry leaders, academic scientists and government research funders; creates a robust open-access data set and biosample library to speed scientific breakthroughs and treatment with its landmark clinical study, PPMI; increases the flow of participants into Parkinson's disease clinical trials with its online tool, Fox Trial Finder; promotes Parkinson's awareness through high-profile advocacy, events and outreach; and coordinates the grassroots involvement of thousands of Team Fox members around the world.?For more information, visit us at? **www.michaeljfox.org**,?**Facebook**,?**Twitter**,?**LinkedIn**.

About Critical Path Institute

Critical Path Institute (C-Path) is an independent, nonprofit organization established in 2005 as a public and private partnership. C-Path's mission is to catalyze the development of new approaches that advance medical innovation and regulatory science, accelerating the path to a healthier world. An international leader in forming collaborations, C-Path has established numerous global consortia that currently include more than 1,600 scientists from government and regulatory agencies, academia, patient organizations, disease foundations, and hundreds of pharmaceutical and biotech companies. C-Path U.S. is headquartered in Tucson, Arizona, C-Path in Europe is headquartered in Amsterdam, Netherlands and C-Path Ltd. operates from Dublin, Ireland with additional staff in multiple other locations. For more information, visit us at c-path.org, LinkedIn, X, Facebook and YouTube.

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Media Contacts:
Kristina Rodriguez
The Michael J. Fox Foundation
krodriguez@michaeljfox.org
212-509-0995

Roxan Triolo Olivas
Critical Path Institute
rolivas@c-path.org
520-954-1634

Kissy Black
C-Path
615.310.1894
kblack@c-path.org