C-Path's PSTC, D-RSC Receive Positive FDA Response for Drug-Induced Skeletal Muscle Injury Biomarkers

Safety biomarkers aim to provide an additional tool for detecting acute drug-induced skeletal muscle injury in phase 1 clinical trials.

TUCSON, Ariz., July 22, 2020 — Critical Path Institute (C-Path) announced today that the Biomarker Qualification Program (BQP) at the Center for Drug Evaluation and Research (CDER) in the U.S. Food and Drug Administration (FDA) issued a positive response to the Letter of Intent (LOI) developed by C-Path's Predictive Safety Testing Consortium (PSTC) and Duchenne Regulatory Science Consortium (D-RSC), for a panel of four safety biomarkers of acute drug-induced skeletal muscle injury.

Currently, drug-induced muscle injury (DIMI) is monitored in clinical trials using blood creatine kinase (CK) and aspartate amino transferase (AST) enzymatic activity in study participants. However, there is an unmet drug development need for new biomarkers since CK and AST lack the desired sensitivity and tissue specificity needed to optimize the identification of drug induced DIMI during clinical trials.

To address this need, PSTC and D-RSC provided scientific evidence in their LOI to support use of a panel of four molecular biomarkers [Skeletal troponin I fast-twitch Type II (TNNI2), Myosin light chain 3 (MYL3), Fatty-acid binding protein 3 (FABP3), and Creatine kinase muscle type (CKM)], as a safety biomarker panel. This panel is intended to aid in the detection of acute DIMI in phase 1 trials in healthy volunteers, in conjunction with AST and CK, when there is an a priori concern that a drug may cause skeletal muscle injury in humans. In its LOI Determination Letter, FDA stated "We have completed our review of your LOI submission . . . and have concluded to accept it into the CDER BQP."

The FDA expressed support for the consortia's intent to pursue biomarker qualification for the DIMI biomarker panel and invited submission of a Qualification Plan — the second stage in the BQP process that details additional clinical validation studies and analysis for the intended Context of Use (COU).
"Finding solutions for unmet needs in drug development is at the core of C-Path's mission," said Program Officer for C-Path's Biomarkers Program and PSTC Executive Director John-Michael Sauer, Ph.D. "Through collaboration across these consortia and their industry members, we are advancing qualification of this biomarker panel to provide drug developers with a novel tool for more accurately detecting DIMI during clinical trials."

This work builds upon extensive nonclinical studies that generated data resulting in a Letter of Support (LOS) from FDA in 2015. "The LOS was an important milestone," explained Warren Glaab, Ph.D., Director of Systems Toxicology at Merck & Co. and PSTC industry member. "Our focus since then has been gathering additional nonclinical and human subject data to demonstrate that this biomarker panel can be translated for use in clinical trials to more accurately detect DIMI."

The biomarker panel could have broad application for drug developers, but for those working to identify treatments and monitor disease progression in patients with neuromuscular diseases such as Duchenne and Becker muscular dystrophy (DMD/BMD), spinal muscular atrophy (SMA), or amyotrophic lateral sclerosis (ALS), it has the potential to be an additional tool.

“As new therapies for DMD, BMD and SMA become available, the proposed biomarker panel may also be useful not only for purposes of safety, but also as diagnostic, prognostic and response biomarkers to provide insight on disease status and response to treatment in patients with these disorders,” said Principal Scientist-Pathologist, Development Sciences-Safety Assessment at Genentech Inc. and PSTC industry member Tanja Zabka, DVM, DACVP, DSP.

As part of the 21st Century Cures Act, passed into law in December 2016, public-private partnerships consisting of government entities, including FDA, the biopharmaceutical industry, health care providers, academic researchers, and patient advocacy organizations have been encouraged to work together to foster innovation in development of new therapies by qualifying new drug development tools that can accelerate the process of making new therapies available to patients. Any groups that would like to join in this effort or have information or data that may be useful can contact John-Michael Sauer (jsauer@c-path.org), or visit C-Path’s website at https://cpathdev4.lotosnile.com/programs/pstc.

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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 dozens of pharmaceutical and biotech companies. C-Path US is headquartered in Tucson, Arizona and C-Path, Ltd. EU is headquartered in Dublin, Ireland, with additional staff in multiple other locations. For more information, visit www.c-path.org and c-path.eu.

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