C-Path's PSTC, D-RSC Receive Positive FDA Response to Plan for Liver Safety Biomarker

Biomarker aims to provide an additional tool for detecting the onset of hepatic injury in clinical trials involving patients with inherited muscle disorders.

TUCSON, Ariz., July 21, 2020 — Critical Path Institute (C-Path) announced today that the Biomarker Qualification Program (BQP) at the Center for Drug Evaluation and Research (CDER) from the U.S. Food and Drug Administration (FDA) issued a positive response to the Qualification Plan (QP) for glutamate dehydrogenase (GLDH) as a safety biomarker for drug-induced liver injury (DILI), developed by C-Path's Predictive Safety Testing Consortium (PSTC) and Duchenne Regulatory Science Consortium (D-RSC).

In this QP, PSTC and D-RSC provided scientific evidence supporting the use of GLDH as an important and accurate measurement of DILI in clinical trials involving patients affected by inherited muscle disorders, such as Duchenne muscular dystrophy (DMD) or idiopathic inflammatory myopathies, and muscle damage caused by strenuous exercise or drug induced muscle injury. In its Determination Letter, the Agency stated, "FDA has completed its review and has agreed to accept your QP."

In clinical trials, alanine aminotransferase (ALT) and total bilirubin (TBil) levels in blood are the current gold standard biomarkers for detecting DILI. Although ALT is a sensitive marker of DILI, this enzyme is also expressed in other tissues, including muscle. This severely limits the reliability of ALT as a biomarker of liver damage in clinical trial subjects with underlying muscle degenerating conditions, such as DMD and related neuromuscular conditions.

"This project was launched to address an unmet need in drug development for increased precision in detection of DILI and serves as a powerful example of advancing translational science from preclinical to clinical use," said PSTC Executive Director John-Michael Sauer, Ph.D. "Through PSTC's and D-RSC's efforts, GLDH's sensitivity and specificity for detection of DILI has been demonstrated in nonclinical studies, and this research can now be translated to application in clinical trials. We are improving the ability to more accurately detect DILI through collaboration and data sharing across consortia and industry members."

FDA expressed support for the consortia's intent to pursue biomarker qualification for GLDH and invited submission of a Full Qualification Package, the final stage that details how the biomarker demonstrates clinical and analytical validity for its intended Context of Use (COU) as a safety biomarker. PSTC and D-RSC propose the qualification of GLDH levels in serum for use as a specific biomarker of DILI in clinical trial subjects with underlying muscle injury or degeneration, in conjunction with standard hepatic injury monitoring biomarkers, such as alkaline phosphatase (ALP) and TBil.

"When ALT levels increase during clinical trials, including in people with underlying muscle disease such as those living with DMD, this can lead researchers to incorrectly conclude a drug candidate is causing liver damage and therefore the study may be discontinued unnecessarily," said C-Path D-RSC Executive Director Jane Larkindale, D.Phil. "Measuring GLDH in addition to traditional biomarkers will provide a new tool for drug developers that generates more accurate and sensitive safety data throughout the clinical trial process."

“GLDH will allow drug developers to properly determine the onset of liver injury in clinical trials for novel therapies to treat patients with muscle disease, where the traditional DILI biomarkers may be confounded by active skeletal muscle injury,” said Jiri Aubrecht, Pharm.D., Ph.D., Scientific Director, Takeda Pharmaceuticals USA Inc. and industry co-director for PSTC.

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 Dr. John-Michael Sauer (jsauer@c-path.org) the point of contact for this project or visit C-Path’s website at https://c-path.org/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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