EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Executive Director

Letter of support for glutamate dehydrogenase, a biomarker of hepatocellular liver injury

On 1 December, 2016 the Applicant Critical Path Global Ltd (C-Path) on behalf of the Predictive Safety Testing Consortium (PSTC) Hepatotixicity Working Group and the Duchenne Regulatory Science Consortium (D-RSC), requested scientific advice for serum glutamate dehydrogenase (GLDH), a novel biomarker of drug induced liver injury pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 29 August – 1 September 2017, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on 11 - 14 September 2017, the CHMP adopted the advice to be given to the Applicant.

On the basis of the qualification advice, the Agency is issuing this Letter of Support to C-Path's PSTC and D-RSC to encourage the further study of serum GLDH for monitoring for hepatocellular liver injury.

In the qualification project being conducted by PSTC, the proposed Context of Use for GLDH is that elevated serum GLDH enzymatic activity is a measure of hepatocellular injury, and can be used in healthy subjects and patients as an adjunct to alanine aminotransferase (ALT), the current standard biomarker used to assess hepatocellular injury, in all stages of drug development. In a clinical situation when ALT increases are observed, the proposal is that GLDH can lend weight of evidence to confirm or rule out hepatocellular injury.

GLDH is highly conserved and constitutively expressed in hepatocytes, while it is expressed in low amounts in non-hepatic tissues including muscle. Published studies and results from unpublished studies submitted by PSTC indicate that GLDH is released into the bloodstream following hepatocellular injury, defined as degeneration/necrosis. Furthermore, unlike ALT, increases in GLDH activity in the serum appear to be highly specific to liver injury and not affected by muscle injury.

When studying GLDH in clinical studies the following aspects should be considered: (1) GLDH activity is proposed to be utilized as a complement to the existing guidance and standard methods for assessing drug induced liver injury (DILI); (2) The mechanism by which GLDH and ALT appear in serum following hepatocellular injury is highly similar, and their enzymatic activity highly correlated in humans and animals with a diversity of liver injuries and diseases; (3) Based on the analysis of several datasets, GLDH activity levels 2.5x and 5x above upper limit of normal (ULN) have been estimated to correspond to 3x and 5x above ULN for ALT, though this still requires further confirmation. These fold changes of GLDH could be utilized, along with the standard hepatic injury monitoring panel, for the assessment of DILI, in the same manner as 3x and 5x ULN ALT.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

With further study and data collection, the intent is to use GLDH to add value to other markers of liver injury including ALT, total bilirubin (TBIL), and alkaline phosphatase (ALP), and to exclude any extrahepatic source of the ALT increase, but not to replace currently used biomarkers of liver injury. Greater experience is needed to confirm the applicability of GLDH to selectively detect DILI in humans.

The Agency supports PSTC's and D-RSC's initiative to encourage investigation of the voluntary and complementary use of serum GLDH, in conjunction with currently used biomarkers of liver injury, as a clinical biomarker of liver injury. The Agency also supports PSTC's generation of additional clinical safety data and plans for further clinical studies to potentially enable formal qualification of GLDH in the future.

When including GLDH in clinical studies, sponsors are encouraged to prospectively discuss any proposed application of the clinical biomarker to decisions made during the course of the study with the European National Authorities responsible for clinical trial authorisation, and/or with the SAWP/CHMP.

Although several suitable test systems are available, no specific serum test system or assay validation process for GLDH is endorsed by this letter. Good scientific and laboratory practices for quality control of the assay test system are imperative. Definition of the assay platform's quantitative range and limits of detection should be established in advance of use.

The Agency encourages the conduct of nonclinical and clinical analyses to evaluate the translational relevance of changes in serum GLDH values and the magnitude of change in serum GLDH that could be considered meaningful in the determination of liver injury when observed in an individual subject and the sharing of this data.

Any groups (academia, industry, government) 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 PSTC point of contact for this project, or view the Critical Path Institute website (www.c-path.org).

Sincerely,

Guido Rasi
Executive Director