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Executive Director

# Letter of Support for skeletal muscle injury biomarkers

On 16 October 2014 the Applicant Critical Path Global Ltd, on behalf of the Predictive Safety Testing Consortium, requested scientific advice for novel biomarkers of drug induced skeletal muscle 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 02 – 05 February 2015, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on 23 – 26 February 2015, 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 the Predictive Safety Testing Consortium (PSTC) to encourage the further study and use of the following plasma or serum proteins in research, nonclinical studies, and early clinical drug development to monitor for skeletal muscle injury in an exploratory context:

- Myosin light chain 3 (Myl3)
- Skeletal muscle troponin I (sTnI)
- Fatty acid binding protein 3 (FABP3)
- Creatine kinase, muscle type (CK-M, the homodimer CK-MM)

These proteins are highly conserved and constitutively expressed in skeletal muscle. Myl3 and sTnI are components of the myofilaments. FABP3 and CK-M are expressed in the sarcoplasm and serve a role in intracellular lipid transport and metabolism, respectively. Published studies and results from unpublished studies submitted by PSTC indicate these proteins are released into the blood stream following skeletal muscle injury, defined as degeneration/necrosis.

To date, the relationship between drug-induced skeletal muscle injury and serum or plasma levels of these proteins has primarily been evaluated in male rats. With further study and data collection, the intent would be to use these biomarkers to add value to total serum creatine kinase (CK; enzymatic assay) and aspartate transaminase (AST) for monitoring skeletal muscle injury in nonclinical and clinical studies; not to replace CK and AST. Greater experience in rats and other species, including

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nonhuman primates, is needed to better understand the applicability of these biomarkers to drug-induced skeletal muscle injury across species, including humans.

The Agency supports PSTC's initiative to encourage the voluntary and complementary use of these serum or plasma proteins in conjunction with AST and CK as exploratory nonclinical and clinical biomarkers of skeletal muscle injury. The Agency also supports PSTC's generation of additional nonclinical toxicology data and plan for exploratory early clinical studies to potentially enable future formal qualification of these biomarkers.

The Agency will consider data collection on these biomarkers to be exploratory in nature.

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

No specific serum or plasma test system or assay validation process for these proteins 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. In addition, it is important to characterize the kinetics of changing levels of candidate biomarkers in the presence of acute self-limited as well as chronic muscle injury. Such investigations should include the study of subjects with no underlying kidney dysfunction as well as others with renal abnormalities in which biomarker clearance may be altered.

The Agency encourages the conduct of nonclinical and exploratory clinical analyses to evaluate the translational relevance of changes in serum or plasma Myl3, sTnI, FABP3 and CKM values and the magnitude of change in serum or plasma Myl3, sTnI, FABP3 and CKM that could be considered meaningful in the determination of skeletal muscle injury when observed in an individual subject.

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.

Sincerely,

Andreas Pott
Deputy Executive Director
European Medicines Agency