



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Executive Director

Letter of Support for PSTC translational Drug-Induced Kidney Injury (DIKI) biomarkers

On 21 November 2013 the Applicant Critical Path Global Ltd. requested the qualification of their translational Drug-Induced Kidney Injury (DIKI) biomarkers pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 07 – 10 July 2014, the SAWP agreed on the advice to be given to the applicant. During its meeting held on 21 - 24 July 2014, the CHMP adopted the advice to be given to the Applicant.

The biomarker letter of support is issued on the basis of the qualification advice.

The package submitted by PSTC is intended to encourage use of urinary osteopontin (OPN) and neutrophil gelatinase-associated lipocalin (NGAL) in nonclinical studies and explore their use in early clinical drug development. The PSTC submission describes a reported relationship between proximal renal tubule degeneration/necrosis and urinary elevations in the levels of these biomarkers in rats.

OPN is reported to be constitutively expressed in the thick ascending limb of the loop of Henle and distal convoluted tubules in both rodents and humans. OPN has been reported to be upregulated in the kidney in response to certain kinds of tissue stress, and in regeneration. NGAL has been reported to be increased within the thick ascending limb of the loop of Henle, distal tubule and collecting duct with nephrotoxic injury in rodents and humans.

Exploratory human data suggests that each of these biomarkers may be able to indicate the presence of acute nephrotoxicity. Neither Urinary OPN nor NGAL have yet been determined to detect nephrotoxicity reliably earlier than standard methods. Greater experience in the clinical setting with OPN and NGAL is needed to understand better the role of these biomarkers in drug development clinical studies and the relationship of these biomarkers to drug-induced renal injury. We are aware that the PSTC/FNIH Biomarkers Consortium Kidney Safety Project Team and Innovative Medicines Initiative Safer and Faster Evidence-based Translation Work Package (SAFE-T/DIKI) programmes are currently conducting studies to qualify urinary OPN and NGAL formally for use in clinical trials. EMA support this initiative.

When including urinary OPN and NGAL 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 SAWP/CHMP. Currently, there is insufficient evidence to support the use of human urinary OPN and NGAL in place of traditional means of monitoring for nephrotoxicity (e.g., serum creatinine, BUN, urinalysis).

No specific urinary OPN or NGAL test system or assay validation process is endorsed by this evaluation. Strong emphasis on applying good scientific and laboratory practices for quality control of the assay test system is imperative. Definition of the assay platform's quantitative range and limits of detection should be established in advance of use.

EMA encourage the conduct of nonclinical and exploratory clinical analyses to evaluate the translational relevance of changes in urinary OPN and NGAL values and the magnitude of change in urinary OPN and NGAL that could be considered clinically meaningful in the determination of kidney injury when observed in an individual subject.

Sincerely,

Guido Rasi
Executive Director
European Medicines Agency