



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: August 20, 2014

ATTN: John-Michael Sauer, Ph.D.
Critical Path Institute
Predictive Safety Testing Consortium
1730 East River Road
Tucson Arizona, 85718

Subject: Biomarker Letter of Support

Dear Dr. Sauer:

Please refer to your submission, provided on behalf of the PSTC, which contains a package 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. Your 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.

Your 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) programs are currently conducting studies to qualify urinary OPN and NGAL formally for use in clinical trials. We support this initiative.

When including urinary OPN and NGAL in early clinical studies, sponsors should prospectively discuss any proposed application of the clinical biomarker to decisions during the course of the study with the appropriate CDER review division. 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.

We 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 meaningful in the determination of kidney injury when observed in an individual subject.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', with a long horizontal flourish extending to the right.

Janet Woodcock, M.D.

Director, CDER

U.S. Food and Drug Administration