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FINAL CONCLUSIONS ON THE PILOT JOINT EMEA/FDA VXDS EXPERIENCE ON QUALIFICATION OF NEPHROTOXICITY BIOMARKERS.

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Final conclusions on the pilot Joint EMEA/FDA VXDS experience on Qualification of Nephrotoxicity biomarkers.

Background

Previously published data on genomic Biomarkers (BMs) of nephrotoxicity (Han et al 2002, Silkensen et al 1997, Verstrepen et al 2001, Amin et al 2004, Thompson et al 2004) support the investigation of a number of accessible protein BMs as exploratory BMs with a high probability of success in diagnosing nephrotoxicity in rats (Han et al 2002) and monkeys (Davis et al 2004).
These include (in addition to the widely known BMs such as urinary albumin, urinary total protein, urinary β_2-microglobulin) the Kidney Injury Molecule (KIM-1) (Han et al 2002, Bailly et al 2002), clusterin (Silkensen et al 1997), urinary Cystatin C (Dharnidharka, Kwon and Stevens 2002) Trefoil factor 3 (TFF 3), as well as changes in the differential expression of other genes included in a toxico-genomic signature for nephrotoxicity (Amin et al 2004, Thompson et al 2004).

The C-Path Predictive Safety Testing Consortium (PSTC), between June 2007 and January 2008, submitted to the FDA and the EMEA, data to support the use of a number of nephrotoxicity BMs for the claims mentioned below.

Qualification claims

The claims of the PSTC representatives for the Urinary BMs submitted were the following:
"… the proposed markers (Kim-1, Albumin, Total Protein, β2-Microglobulin, Cystatin C, Clusterin and Trefoil Factor 3) 'add information' to serum creatinine and BUN, while six of the seven were also shown to outperform one or both of these clinical chemistry markers.
We claim that these kidney BMs correlate to either tubular histomorphologic alterations or to glomerulopathy with functional tubular involvement.
We make biomarker claims that apply more accurately to acute drug-induced kidney histomorphologic change which are supported by our data rather than more traditional chronic kidney injury.
We claim voluntary use of these BMs by sponsors in preclinical GLP studies.

In addition, when taken together with published peer-reviewed clinical data as sensitive BMs of kidney injury in humans, we claim voluntary use of several urinary BMs (Kim-1, Albumin, Total Protein, β2-Microglobulin, and Cystatin C) as bridging markers for early clinical studies on a case-by-case basis when concerns are generated by findings in GLP animal toxicology studies".

Data submitted

The data submission occurred in consecutive waves between June 2007 and January 2008 and included:

- Information and analyses of data from short term (up to 3 weeks) rat GLP toxicology studies (Novartis: 19, Merck: 20 and FDA:4 studies) aiming at the identification of BMs of drug-induced acute kidney toxicity.
- Data on the analytical validation of the methodologies used
- Review of the scientific literature pertaining to exploratory studies in human clinical context relevant to some of the BMs (except Urinary clusterin and Urinary Trefoil Factor 3) presented for this joint FDA/EMEA pilot process.

The FDA and the EMEA contributed to the evaluation via the ad hoc appointed pilot Biomarkers qualification teams (BMQTs) providing (via written procedures and Joint Videoconferences with the FDA and the PSTC representatives) elements for gap analysis, questions on the statistical evaluations and drafting the preliminary conclusions.

Summary of studies conducted

	Novartis	**Merck**	**FDA**
Rat strain	Han Wistar	Sprague Dawley, except for two studies	Sprague Dawley
Sex	Male	Male (Only one study (carbapenem-TC) with males and females)	Male
Animal number/group	6	4-6	3-6
Number of nephrotoxicants	8	11	4
Common nephrotoxicants	cisplatin gentamycin	cisplatin gentamycin	cisplatin gentamycin
Number of non-nephrotoxicants	2	9	0
BMs used	BUN, serum Cr KIM-1, clusterin, total protein, cystatin, β2-microglobulin	BUN, serum Cr, KIM-1, albumin, TFF-3	BUN, serum Cr, KIM-1,

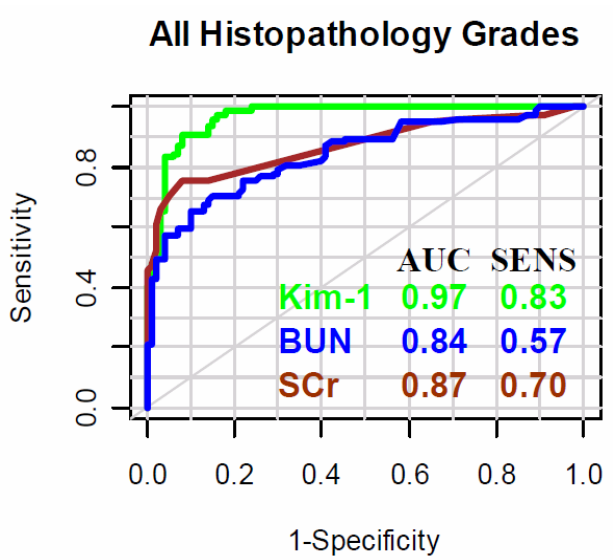
The final discussions mainly focussed on the inclusive ROC analyses that presented all of the data from the different studies.

Performance of each new biomarker versus the accepted standards of BUN and serum creatinine was evaluated by comparison of the area under the curve (AUC) of the ROC analysis for each new biomarker with the similar data obtained for BUN and creatinine.
ROC curves were generated both for data merged from all positive histopathology scores for all studies by study site, as well as for data from subset ranges of these scores.

The ROC curves for the complete KIM-1 and albumin data from Merck are shown in Figure. 1, while the ROC curves for the complete KIM-1, clusterin, total protein, β-2 microglobulin, and cystatin data from Novartis are shown in Figure 2.

Fig. 1: *Inclusion* model - All Histopathology Grades – All Merck data
AUC (area under the curve) SEN (sensitivity at 95% specificity) are shown. Note that compound treated animals with grade 0 histopathology were *included* for this analysis. ROC curves were generated using all histopathology grades. Total number of animals: 178 (KIM-1), 700 (Albumin).

KIM-1



Albumin

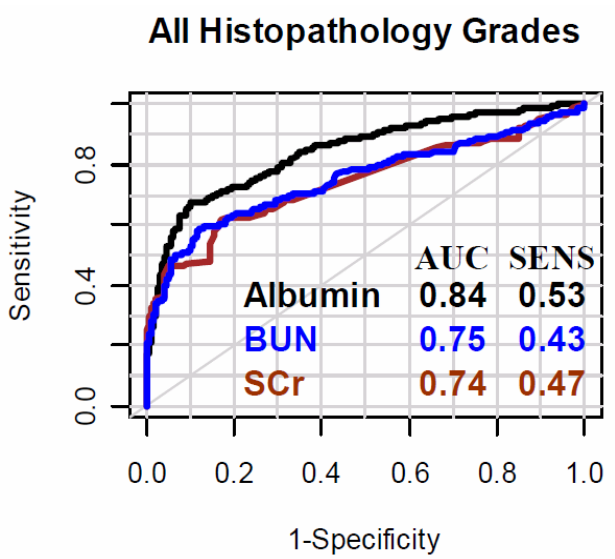
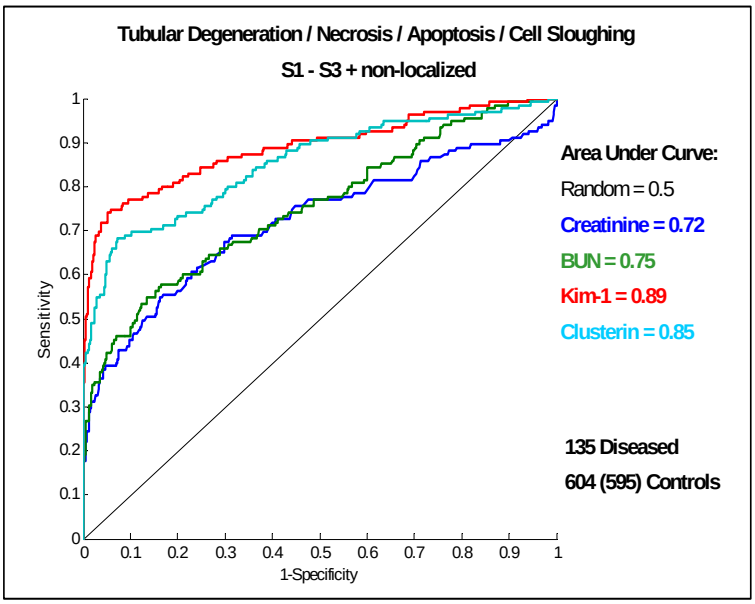


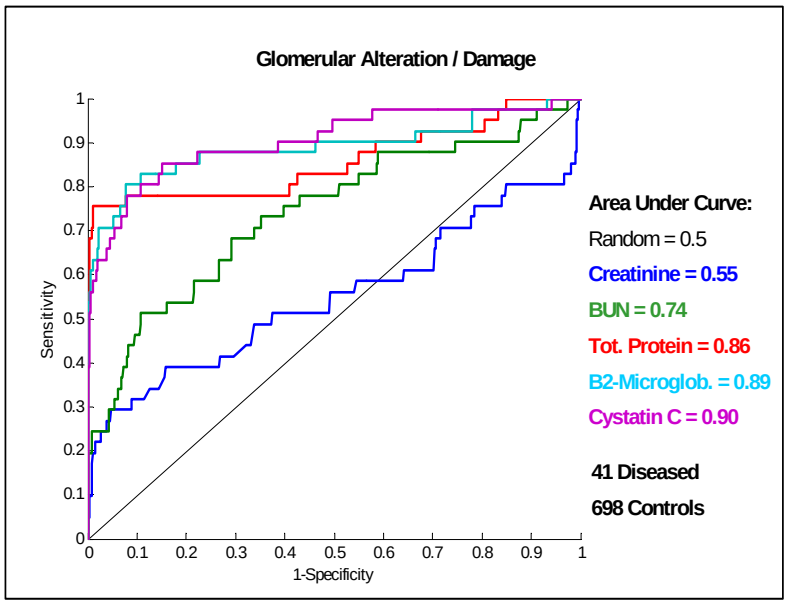
Fig 2. *Inclusion* model - All Histopathology Grades – All Novartis data

ROC inclusion curves of tubular and glomerular markers. The analysis using animals with all histopathology grades (0-5) included compound treated animals with grade 0 histopathology. The AUC (area under the curve) values and the number of animals (KIM-1 in parentheses) are listed. Total number of animals: 739 (clusterin, total protein, cystatin, β2-microglobulin), 730 (KIM-1).

Pathology of "Tubular Damage"



Pathology of "Glomerular Damage"



Limitations of the data set

The BMQT considered that the limitation of the data package submitted for all the identified BMs (including Kim 1, urinary Clusterin, urinary Tff-3, urinary Cystatin C) is that, although the PSTC provided information on dose- and time- dependent changes in the biomarkers and the appearance of histopathological alterations during periods of dosing, there are insufficient data to establish a clear correlation between the BMs and the evolution of the nephrotoxic alterations over time, as documented by histopathology. The reversibility of the biochemical changes is insufficiently correlated with kidney function recovery. Therefore the use of these BMs in "monitoring" renal toxicity at this stage is not sufficiently demonstrated.

Additional limitations were identified and included:
Data to support qualification was often collected retrospectively; since urinary creatinine is affected by water and food consumption, the data for individual animals should have included body weight, food consumption and water consumption data for all studies; histopathology scores were based on evaluation of only one section of one kidney; data were insufficient to establish a temporal correlation between lesions and BMs levels; data were insufficient to demonstrate that specific BMs can determine the location of the injury.

Conclusions

Non-clinical context:

- The urinary kidney BMs (Kim-1, Albumin, Total Protein, β2-Microglobulin, urinary clusterin, Urinary Trefoil Factor 3 and urinary Cystatin C) are considered acceptable in the context of non-clinical drug development for the detection of acute drug-induced nephrotoxicity, either tubular or glomerular with associated tubular involvement.
- They provide additional and complementary information to BUN and serum creatinine to correlate with histo-pathological alterations considered to be the gold standard.
- Additional data on the correlation between the BMs and the evolution and reversibility, of acute kidney injury are needed. Also, further knowledge on species-specificity is required.

Clinical context:

- It is recognised that it is worthwhile to further explore, in early clinical trials, the potential of Kim-1, Albumin, Total Protein, β2-Microglobulin, Urinary clusterin, Urinary Trefoil Factor 3 and urinary Cystatin C as clinical BMs for acute drug-induced kidney injury. Until further data are available to correlate the BMs with the evolution of the nephrotoxic alterations, and their reversibility, their general use for monitoring nephrotoxicity in clinical setting cannot be qualified.
- The use of these renal biomarkers in clinical trials may be considered on a case-by-case basis in order to gather further data to qualify their usefulness in monitoring drug-induced renal toxicity in man.

Ways how to best implement these biomarkers in a further non-clinical and/or clinical development program, can be discussed on a case by case basis in the context of the new EMEA qualification advice (see http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf).