A Collaborative Approach for the Qualification of Novel Kidney Biomarkers with the Regulatory Authorities

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Background

Drug-induced kidney injury (DIKI) is not an uncommon adverse event in drug development. The challenge being the late identification of Acute Kidney Injury due to weaknesses in the current standards (i.e. serum creatinine (sCr) and blood urea nitrogen (BUN)) which may not be significantly changed until 2/3 of the kidneys function has already been lost.

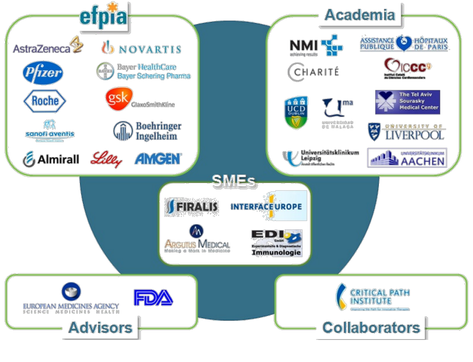
Over the last three years there has been great progress with preclinical qualification processes for kidney biomarkers. The PSTC and ILSI HESI have both had rat kidney biomarkers qualified by both the FDA and EMA. These landmark qualifications mean that drug companies may now use certain novel preclinical markers for **real** decision making within their drug discovery process.

Objectives

- Qualify biomarkers that detect DIKI earlier than the currently used standards
- Gain scientific acceptance and regulatory endorsement for the use of these biomarkers in defined clinical contexts
- Build a comprehensive Bio-bank of samples and data for further dissemination at project completion

SAFE-T Consortium

The principal objective of this new project is to collect and generate sufficient **clinical** data from a number of candidate kidney biomarkers, that will provide convincing evidence for the health authorities to endorse these biomarkers for the detection and monitoring of drug induced kidney injuries in specific clinical situations. To address this, a European-based partnership called the **SAFE-T Consortium** was formed from 20 participants from the pharmaceutical industry, small-medium enterprises, academic institutions and clinical units.



Biomarkers Selected

SAFE-T are using commercially available assays for the candidate biomarkers selected where available. Through a series of low and high bar validation processes the markers have been assessed for their suitability for entry into the clinical sample assessment. SAFE-T selected the above biomarkers through a comprehensive analysis of over 50 candidates. These markers were assessed for factors such as; published clinical data, published preclinical data, availability of assay, stability, assay and analyte kinetics and stability, IP suitability, etc. From this list of 50, 21 biomarkers were chosen for assessment. For some of the markers that are available on multiple technologies (ELISA, Luminex, Mesoscale, etc.) the consortium has undertaken dual technology assessment.

Analyte name	Platform	Status
Cystatin C Urinary/Serum	Luminex (NMI-RBM)	Validated
Cystatin C Urinary/Serum	ELISA (Biovendor)	Validated
Alpha 1 Microglobulin (Urine)	Luminex (NMI-RBM)	Validated
Alpha 1 Microglobulin (Urine)	ELISA	Validated
Kidney Injury Molecule 1 (Urine)	Luminex (NMI-RBM)	Validated
Kidney Injury Molecule 1 (Urine)	ELISA (RnD Systems)	Validated
Glutathione S Transferase alpha (Urine)	Luminex (NMI-RBM)	Validated
Glutathione S Transferase alpha (Urine)	ELISA (Argutus)	Validated
NGAL Lipocalin 2 Urinary/Serum	Luminex (NMI-RBM)	Validated
NGAL Lipocalin 2 Urinary/Serum	ELISA (Bioporto)	Validated
Timp-1 (Urine)	Luminex (NMI-RBM)	Validated
Timp-1 (Urine)	ELISA (Biovendor)	Validated
Clusterin Urinary (Urine)	Luminex (NMI-RBM)	Validated
Clusterin Urinary (Urine)	ELISA (Biovendor)	Validated
Liver Fatty Acid Binding Protein (Urine)	ELISA (CMIC)	Validated
Glutathione S Transferase pi (Urine)	ELISA (Argutus)	Validated
Retinol Binding Protein (Urine)	ELISA (NMI)	Validated
Urinary MCP1 (Urine)	ELISA (NMI)	Validated
Osteopontin (Urine)	Luminex (NMI-RBM)	Validated
Connective Tissue Growth Factor (Urine)	Luminex (NMI-RBM)	Validated
Interleukin 18 (Urine)	ELISA (NMI)	Validated
Collagen IV Urinary	ELISA (Daiichi)	Validated
Calbindin D28 (Urine)	Luminex (NMI-RBM)	Validated
TFF3 (Urine)	Luminex (NMI-RBM)	Validated
Aquaporin II (Urine)	LC-MS (Sanofiaventis)	Developed
Podocin (Urine)	LC-MS (Sanofiaventis)	Developed

Clinical Trial Approach

- Collect urine and serum samples in an exploratory series of prospective clinical trials for key drugs affecting certain pathologies and the relevant controls as well as a healthy volunteer cohort
- Establish adjudication panel to examine every patient series of data and charcterize as AKI/non-AKI with relevant statistical power to make decisions on suitability of the biomarkers for potential contexts of use
- Assess the performance of the biomarkers using the AKIN criteria as gold standard to determine which markers will progress to a larger confirmatory clinical trial later in early 2013

Healthy Volunteers	Cisplatin Study	Contrast Media Study	Acute Glomerulonephritis Study
N = 24	N = 100 patients	N = 200 patients	N = 200 patients
6 time-points	7 time-points	4-7 time-points	3 time-points
Spot urine & Serum	Spot urine & Serum	Spot urine & Serum	Spot urine & Serum

Stage Gate Analysis

To optimize the assessment of these biomarkers it was decided to investigate a subset of the exploratory studies to enable SAFE-T to drop markers with high variability in healthy volunteers and no or minimal responses to drug induced kidney injury (according to established criteria, i.e. AKIN, KDIGO, RIFLE). A clinical adjudication committee was established and investigated every patient's clinical results to identify AKI patients and exclude patients with protocol failure or too few samples / data collected.

Study/ population	Number of subjects tested	Time-points per subject
Acute GN patients	50	1
CIN study	All AKI patients selected by adjudication committee during stage gate analysis (128 patient recruited)	4 to 7
Cisplatin study	All AKI patients selected by adjudication committee (33 patients recruited)	7
Healthy volunteers	24	6
CKD patients	40	2
Cancer control patients	20	2
Transplant patients	50	0

At an interim stage of the exploratory studies (128 contrast media patients and 33 cisplatin patients recruited), the clinical adjudication committee have investigated the individual patient datasets from the contrast and cisplatin treatment arms and rigorously assessed their clinical data and categorized the patients as AKI and non-AKI. It is anticipated that these cohorts of samples will be sent from the SAFE-T biobank in Barcelona to the individual testing sites (Argutus – Dublin, NMI – Tübingen and Sanofi Aventis – Paris) in November for processing and results transferred to the biostatistician work package in early January

Study/ population	Subjects Assessed	Number of AKI Subjects	Incidence Rate
Contrast Media	128	20 (KDIGO criterion)	16%
Cisplatin	33	8 (KDIGO criterion)	24%

Next Steps

- Complete the assessment of the candidate biomarkers with the stage gate cohort of samples
- Select the leading candidates to proceed to the confirmatory clinical study(ies) and drop those that are too variable in a healthy cohort or too insensitive with clear AKI cases as identified by adjudication committee.
- Analyze the selected biomarkers in the entire population of the exploratory clinical studies
- Seek regulatory advice and approval (with the FDA and EMA) for the proposed confirmatory study(ies)
- Plan prospective confirmatory trials. Currently two trials for the confirmatory phase are anticipated
- Start prospective trial(s) and have shortlisted biomarkers assessed and analyzed within 12 months
- Prepare a qualification submission to the regulatory authorities with the leading biomarker(s) that demonstrate value in identification of drug induced kidney injury and have clinical utility.