IMI project - SAFE-T
An European consortium approach to renal safety biomarkers

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On behalf of DIKI subgroup
Introduction to SAFE-T

- **Safer And Faster Evidence-based Translation**
- **Innovative Medicines Initiative - Qualification of Translational Safety Biomarkers**
- Partnership of pharmaceutical companies, academic centres, small business enterprises having open dialogue with regulatory authorities
- 5 year project started in June 2009
- 36M € ($44M) research budget
  - Funding from European Commission with in-kind contributions from Pharma
SAFE-T participants

Academia

AstraZeneca
Novartis
Pfizer
Roche
Bayer HealthCare
Bayer Schering Pharma
gsk
GlaxoSmithKline
Boehringer Ingelheim
Sanofi
Almirall
Amgen

SMEs

FIRALIS
INTERFACE EUROPE
Argus Medical
EVID GmbH

Advisors

European Medicines Agency
FDA

Collaborators

Assistance Publique Hôpitaux de Paris
Universidad de Malaga
Universität Köln
University of Liverpool
Universitätsklinikum Leipzig
Tel Aviv Sourasky Medical Center

SAFE-T Renal Safety Biomarkers ProjectERA-EDTA Meeting, Paris 2012
The SAFE-T Project Objectives

• To evaluate utility of safety biomarkers for monitoring organ safety in humans.
• To develop assays and devices for clinical application of safety biomarkers.
• To compile evidence to qualify safety biomarkers for regulatory decision-making in clinical drug development.
• To gain evidence for how safety markers may be used in disease diagnosis and in clinical practice (e.g. intensive care units).
Three areas of focus for safety markers

- **Drug-Induced Kidney Injury**
  - Serum Creatinine + BUN are significantly increased only when 50% of kidney function is lost.

- **Drug-Induced Liver Injury**
  - Transaminases are not specific and or predictive of who will recover vs. develop liver failure.

- **Drug-Induced Vascular Injury**
  - There are currently no clinical biomarkers to monitor vascular injury.

- Overall objective of SAFE-T programs
DIKI Biomarker Qualification Strategy

**Literature**
- Databases
- SAFE-T sources

Select

**Biomarker step 1 list**
Evaluation

**Biomarker step 2 list**

**Biomarker step 3 list**
- Regulatory advice
- Assay availability / development
- Biomarker step 3 list
- Assay / stat analysis / select specific+sensitive BMs

**Biomarker step 4 list**
- Regulatory advice
- Assay / stat analysis / select specific+sensitive BMs
- Biomarker step 4 list
- Assay / stat analysis / select specific+sensitive BMs

**Exploratory phase**

**Current status**
Background variability
Thresholds (ROCs)

**Confirmatory phase**

**Current status**
Qualification

**Samples**
- Healthy volunteers
- Patients with x-disease
- Patients with non-x disease
- Patients on x-toxic drugs

**Q2 2009**

**Q1 2010**

**Q4 2012**

**Q4 2014**

**Regulatory approval**

**Submit to health authorities**

**SAFE-T sources**

**Renal Safety Biomarkers ProjectERA-EDTA Meeting, Paris 2012**
Overall DIKI Project Timelines

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>SAFE-T kick-off</td>
<td>Biomarker selection process &amp; Initial clinical plans</td>
<td>Biomarker assay development/ validation</td>
<td>Exploratory studies protocol preparation</td>
<td>Regulatory meetings</td>
<td>Acute GN study</td>
</tr>
</tbody>
</table>

SAFE-T Renal Safety Biomarkers ProjectERA-EDTA Meeting, Paris 2012
1. Selection process

Candidate biomarker selection
- Literature evidence
- Previous experience in rat studies
- Pharma company databases

Renal injury populations
- Review of drugs that cause renal injury
- Prevalence/feasibility/region of kidney injury
- Shortlist based on kidney region & feasibility
<table>
<thead>
<tr>
<th>Type of biomarker</th>
<th>Biomarker name</th>
<th>Main significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional biomarkers</td>
<td>Microalbumin</td>
<td>Marker of impaired proximal tubular re-absorption</td>
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<tr>
<td></td>
<td>α-1 microglobulin</td>
<td>Marker of impaired proximal tubular re-absorption (and indirectly glomerular injury)</td>
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<tr>
<td></td>
<td>Cystatin C</td>
<td>Evaluation of glomerular filtration rate (serum)</td>
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<tr>
<td></td>
<td>Retinol Binding Protein-4 (RBP-4)</td>
<td>Marker of impaired proximal tubular re-absorption</td>
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<tr>
<td>Tissue injury leakage markers</td>
<td>N-acetyl-β-D-glucosaminidase (NAG)</td>
<td>Marker of proximal tubular injury</td>
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<tr>
<td></td>
<td>Glutathione-S-transferase-α (GST-α)</td>
<td>Marker of proximal tubular injury</td>
</tr>
<tr>
<td></td>
<td>Glutathione-S-transferase-π (GST-π)</td>
<td>Marker of distal tubular injury</td>
</tr>
<tr>
<td></td>
<td>Liver-type fatty acid binding protein (L-FABP)</td>
<td>Marker of proximal tubular injury</td>
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<tr>
<td></td>
<td>Collagen IV</td>
<td>Marker of glomerular injury</td>
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<tr>
<td></td>
<td>Podocin</td>
<td>Marker of glomerular injury</td>
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<tr>
<td></td>
<td>Nephrin</td>
<td>Marker of glomerular injury</td>
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<td></td>
<td>Aquaporin-2</td>
<td>Marker of collecting duct injury</td>
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<tr>
<td></td>
<td>Calbindin D28</td>
<td>Marker of injury to distal regions of nephron and collecting ducts</td>
</tr>
<tr>
<td>Tissue injury response markers</td>
<td>Kidney injury molecule-1 (KIM-1)</td>
<td>Marker of proximal tubular injury/regeneration</td>
</tr>
<tr>
<td></td>
<td>Clusterin</td>
<td>Marker of tubular injury/regeneration (no apparent specific nephronal localization)</td>
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<tr>
<td></td>
<td>Neutrophil gelatinase associated lipocalin (NGAL)</td>
<td>Marker of tubular (mainly proximal) injury</td>
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<tr>
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<td>Trefoil Factor 3 (TFF3)</td>
<td>Marker of proximal tubular injury</td>
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<tr>
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<td>Osteopontin</td>
<td>Marker of injury to distal regions of nephron</td>
</tr>
<tr>
<td></td>
<td>Tissue inhibitor of metalloproteinase-1 (TIMP-1)</td>
<td>Marker of interstitial fibrosis and tubular injury</td>
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<tr>
<td></td>
<td>Connective Tissue Growth Factor (CTGF)</td>
<td>Marker of interstitial fibrosis</td>
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<tr>
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<td>Interleukin-18 (IL-18)</td>
<td>Marker of inflammation</td>
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<tr>
<td></td>
<td>Monocyte chemoattractant protein-1 (MCP-1)</td>
<td>Marker of inflammation</td>
</tr>
</tbody>
</table>
2. Exploratory studies

- Preparation for study conduct
  - Assay development
  - Setting up of biobank facility for clinical samples
  - Academic sites selected
  - eCRF design and database set-up

- Design of clinical studies
  - Renal injury studies
  - Control population studies
2. Exploratory phase: main studies

• Baseline studies
  • Healthy volunteer study
  • Chronic kidney disease study
  • Non-renal disease patient samples

• Renal injury studies
  – Proximal tubular damage studies
    • Cisplatin in cancer patients study
    • Contrast induced nephropathy study
  – Glomerular damage studies
    • Acute glomerulonephritis patient study

NOTE: Nephrotoxicity studies will be in patients receiving Standard of Care treatment
2. End of exploratory phase

- Results interpretation
  - Selection of biomarkers with good sensitivity & specificity
  - Setting of appropriate thresholds for injury

- Planning for confirmatory phase studies
  - Identifying appropriate populations
  - Optimising study designs (endpoints, sampling timepoints, sample size calculation, etc.)

- Interactions with Regulatory Agencies
  - Presenting data from exploratory studies
  - Sharing plans for confirmatory studies to gain buy-in
3. Confirmatory studies

- Confirmatory phase 2013-14
  - Intent is to conduct 1-2 confirmatory studies
  - Choice of populations and studies TBD
    - proximal conv. tubular ± glomerular injury study(ies)
    - co-ordinate with PSTC to avoid duplication of effort
  - Study design(s) based on exploratory study results
3. Confirmatory phase: other studies

- **Baseline studies**
  - Additional healthy volunteer samples
  - Non-renal disease patients studies

- **Specificity studies**
  - Organ injury studies done as part of liver and vascular injury SAFE-T projects

- **Supportive studies**
  - Renal biopsy study in transplant patients
  - *Study in patients in ICU setting?*
  - *Other supportive studies?*

Studies started in exploratory phase but main body of work will be conducted in confirmatory phase.
Exploratory Phase Studies
Healthy Volunteer Study

- Single centre, non-drug study: completed
- Design:
  - 25 healthy subjects
    - 12 male, 13 female subjects:
      - 6+7 subjects 18-45 years old
      - 6+6 subjects 46-65 years old
  - 3 study periods
    - Day 0, Day 7, Day 28
    - In each period:
      - 6 blood samples collected over 24H
      - 1 spot urine plus urine collections over 24H (0-4, 4-12, 12-24h)
    - Blood analysed for serum creatinine, BUN, serum cystatin C
    - Urine samples analysed for all urinary biomarkers
- Assay work ongoing: results expected 3Q2012
Renal Injury Studies: Objectives

– To collect blood and urine samples in target population and control subjects.
– To characterise between-and within-subject variability of novel biomarkers vs. BUN/ serum creatinine.
– To compare patterns of novel biomarker changes relative to BUN/ serum creatinine to:
  • select candidate biomarkers to progress to confirmatory stage and establish cut-off values for these biomarkers.
  • characterise the time course of biomarker changes to optimise the study design of confirmatory studies.
Populations

• **Group A**: patients with various cancers who are scheduled to start high dose cisplatin therapy.
  \[N=100\]
  [20 subjects enrolled to date]

• **Group B**: control patients with similar cancers treated with local radiotherapy or non-nephrotoxic drugs.
  \[N=20\]
  [18 subjects enrolled to date]

• **Group C**: non-treatment healthy volunteers.
  \[N=20\]
  [25 subjects enrolled]

• *Ongoing study: anticipated completion 1H2013*
Patients with cancer due to receive cisplatin chemotherapy as Standard of Care

Pre-Tx  Cis.  Post-1\textsuperscript{st} cycle of cisplatin

Urine & blood samples
(BUN/ s creatinine, serum and spot urine samples for novel markers)

Control subjects: two samples taken 4 days apart
Populations

- **Group A**: patients with symptoms of acute GN and renal biopsy-confirmed diagnosis.
  - *N*=100 patients with confirmed acute GN
  - [71 subjects enrolled to date]

- **Group B**: control patients with chronic renal impairment due to polycystic kidney disease.
  - *N*=20-50
  - [32 subjects enrolled to date]

- **Group C**: healthy volunteers.
  - *N*=20
  - [25 subjects enrolled]

- *Ongoing study: anticipated completion 3Q2012*
Patients presenting with symptoms suggestive of acute GN

Symptom onset

Renal biopsy

Note: no baseline sample

Urine & blood samples within 3-6 month period
(BUN/ s creatinine, serum and spot urine samples for novel markers)

Control subjects will have 2 samples taken over 2-4 week period
Contrast-Induced Nephropathy Study

Populations

• **Group A**: High-risk subjects: patients with chronic renal impairment and 1 other factor predisposing to CIN and scheduled for coronary angiography.
  \(N=200\) patients
  [86 subjects enrolled]

• **Group B**: Low-risk subjects: patients scheduled for contrast radiology study at low risk of developing CIN.
  \(N=20\) patients

• **Group C**: non-treatment healthy volunteers.
  \(N=20\)
  [25 subjects enrolled]

*Ongoing study: anticipated completion 4Q2012*
Patients scheduled to undergo contrast injection as part of planned radiological investigation

Contrast administration

B/L Post-contrast administration

4-6H 24H 48H D7 D29 D91

Urine & blood samples
(BUN/creatinine, serum and spot urine samples for novel markers)

Control subjects: 2 samples taken 4 days apart
Chronic Kidney Disease Study

• Supportive study – will continue into confirmatory phase
• Main objective
  – Collect blood and urine samples in CKD patients.
• Study population
  – \( N = 200 \) patients with diabetic nephropathy.
• Study design
  – Subjects are participating in a Phase 2 Pharma drug study.
  – 1\(^{st} \) sample taken at baseline before start of randomised treatment
  – 2\(^{nd} \) sample taken 2 weeks post-cessation of randomised treatment
    (drug will have washed out by this time)
• Samples will be analysed for novel biomarkers
• **Ongoing study: anticipated completion 4Q2012**
  [130 subjects enrolled to date]
Renal Transplant Biopsy Study

• Supportive study – will continue into confirmatory phase
• Main objective
  – correlate DIKI biomarkers and renal histopathological findings.
• Study population
  – $N = 400$ post-renal renal transplant patients.
    • patients scheduled to have a renal biopsy
      – Routine biopsy
      – Biopsy to determine cause of potential graft failure
• Study design
  – eligible patients have blood and urine samples taken prior to biopsy on day of planned procedure
• Endpoints
  – DIKI biomarker patterns correlated to renal biopsy findings
• Ongoing study: anticipated completion 2014
  [50 subjects enrolled to date]
Summary

• Consortium-based approach to safety biomarker qualification working with Regulatory Agencies and academic community
• Novel kidney biomarkers of interest chosen with new assays developed as necessary
• First healthy volunteer study completed with additional samples collected in other studies
• Three exploratory phase studies are ongoing to assess renal markers of glomerular damage and renal tubular injury
Next Steps

• Completion of exploratory studies
• Analysis of novel biomarker data and determine which are appropriate to test in confirmatory phase
  – Interactions with PSTC to align strategies
• Design of confirmatory studies with Regulatory Agency advice