IMI project - SAFE-T

An European consortium approach to renal safety biomarkers

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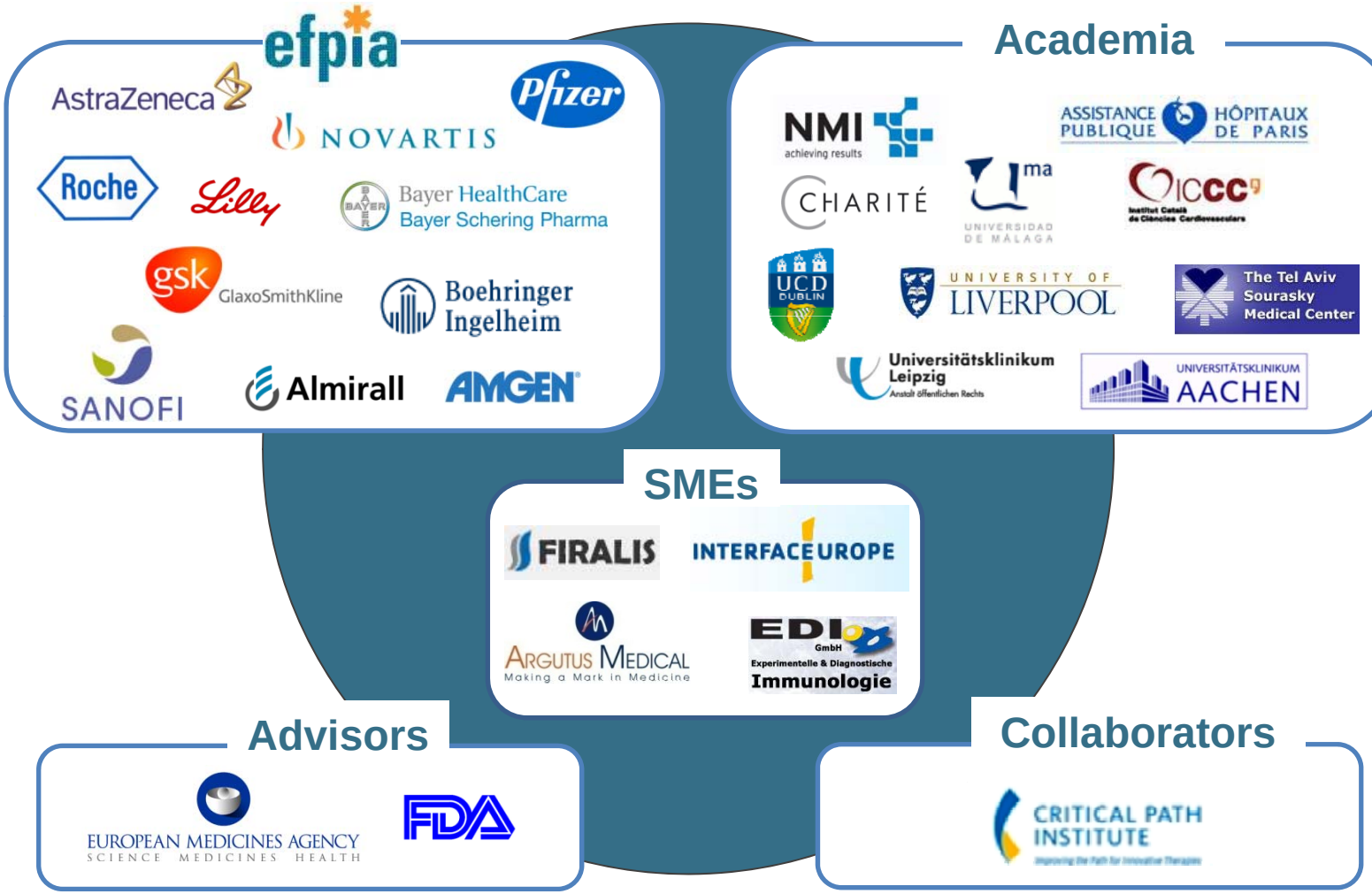
On behalf of DIKI subgroup

SAFE-T

Introduction to SAFE-T

- **S**afer **A**nd **F**aster **E**vidence-based **T**ranslation
- **I**nnovative **M**edicines **I**nitiative - 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



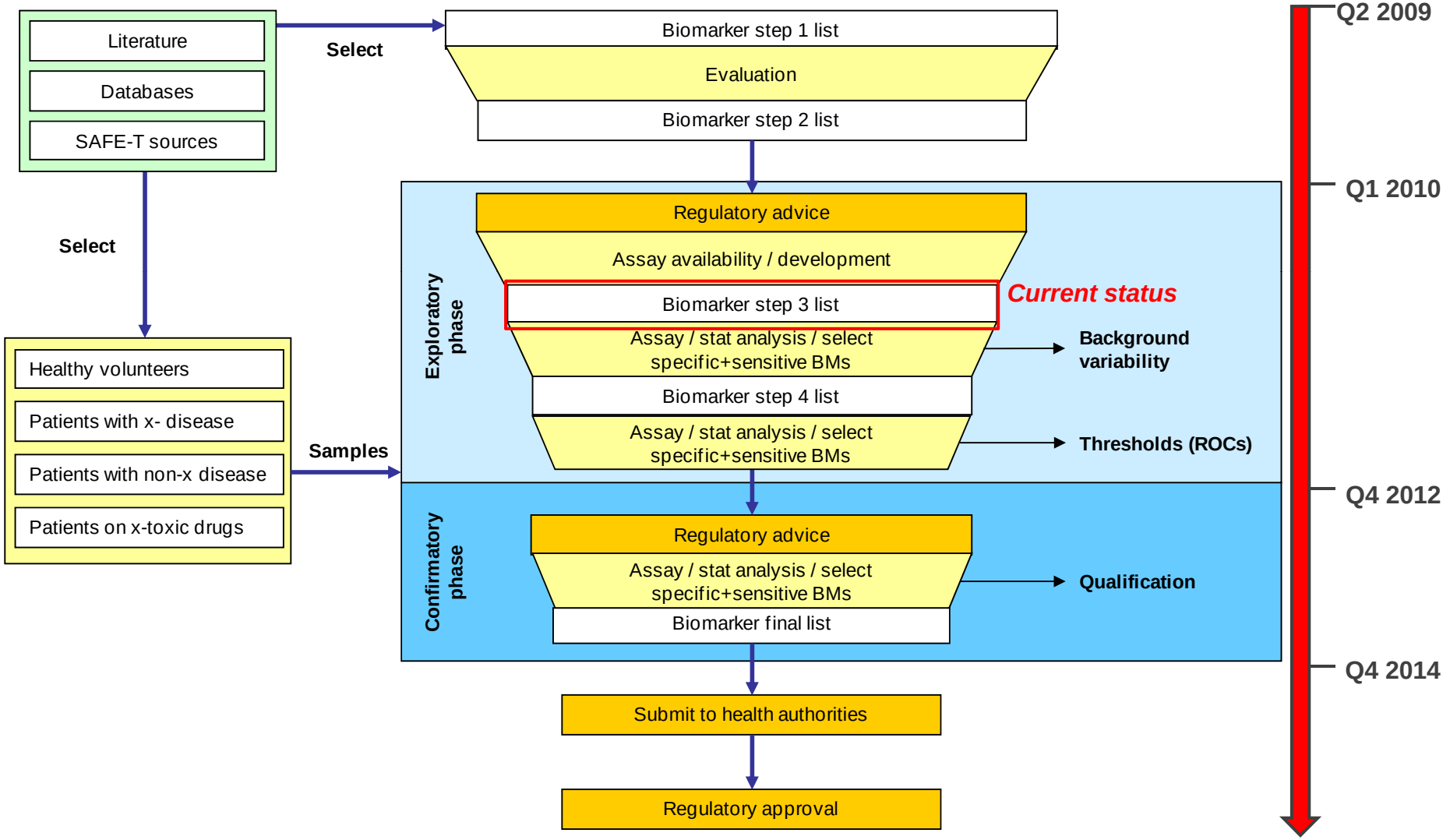
The SAFE-T Project Objectives

- 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).

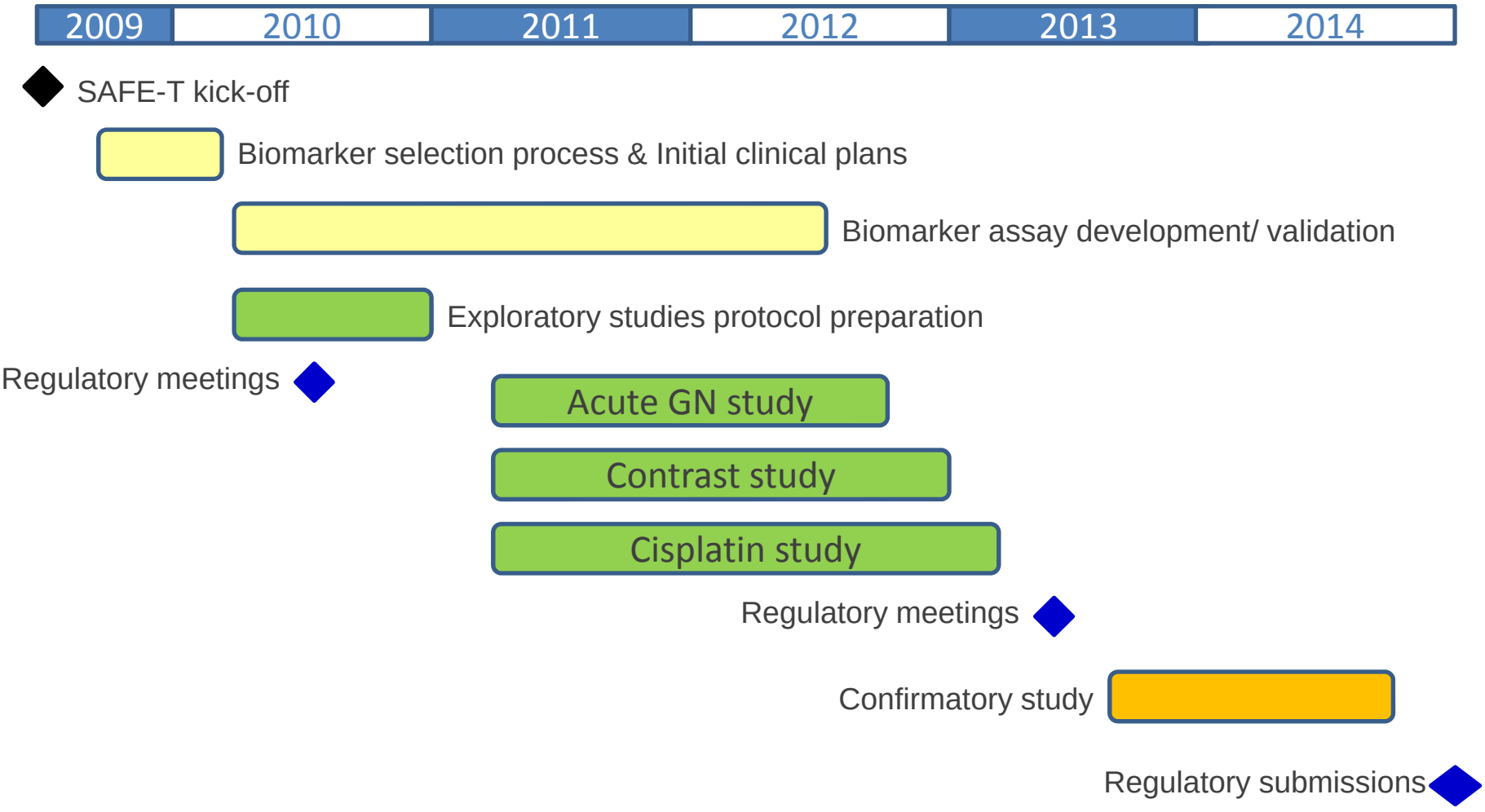
Three areas of focus for safety markers

- **D**rug-**I**nduced **K**idney **I**njury
  - Serum Creatinine + BUN are significantly increased only when 50% of kidney function is lost.
- **D**rug-**I**nduced **L**iver **I**njury
  - Transaminases are not specific and or predictive of who will recover vs. develop liver failure.
- **D**rug-**I**nduced **V**ascular **I**njury
  - There are currently no clinical biomarkers to monitor vascular injury.
- Overall objective of SAFE-T programs

DIKI Biomarker Qualification Strategy



Overall DIKI Project Timelines



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

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

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

  } Establish normative range and variability of each marker

- Renal injury studies
  - Proximal tubular damage studies
    - Cisplatin in cancer patients study
    - Contrast induced nephropathy study

    } Longitudinal case control studies

  - Glomerular damage studies
    - Acute glomerulonephritis patient study

    } Cross-sectional case control 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.

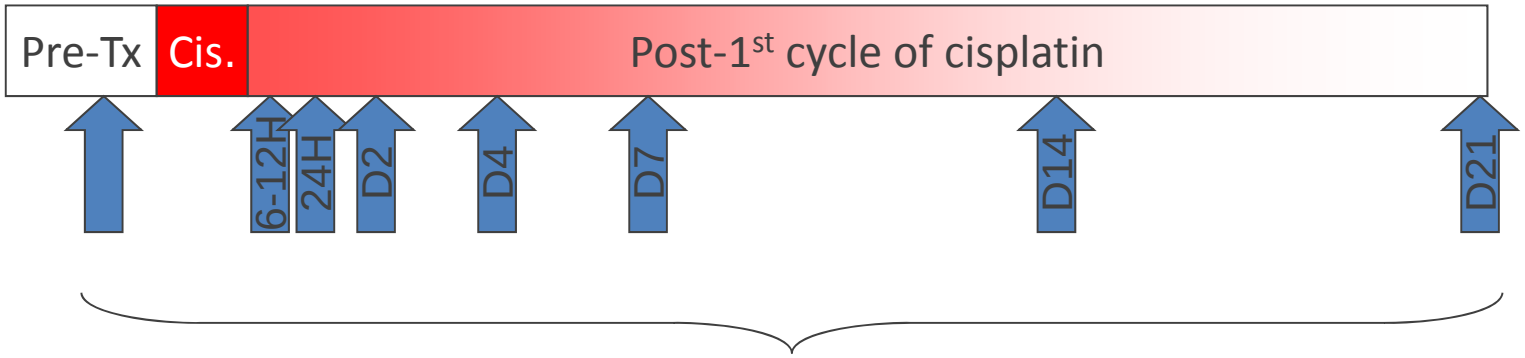
Cisplatin Study

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*

Cisplatin Study Design

Patients with cancer due to receive cisplatin chemotherapy as Standard of Care



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

Control subjects: two samples taken 4 days apart

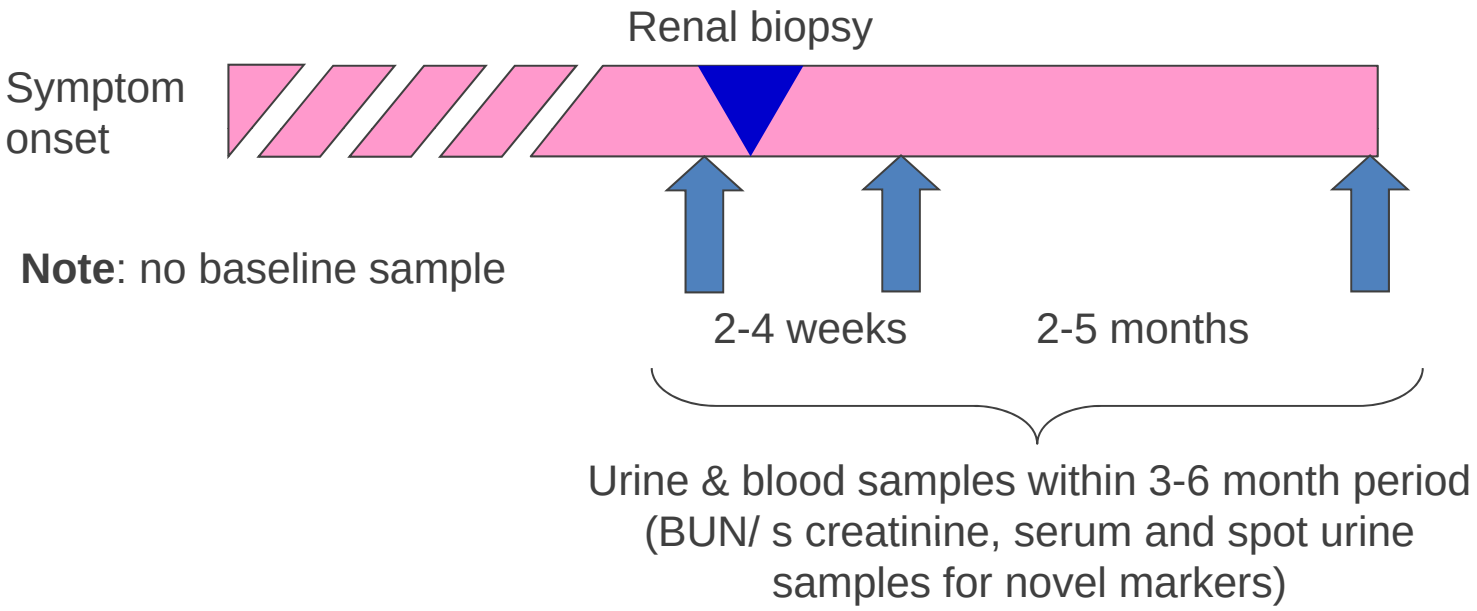
Acute Glomerulonephritis Study

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*

Acute Glomerulonephritis Study Design

Patients presenting with symptoms suggestive of acute GN



Note: no baseline sample

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]

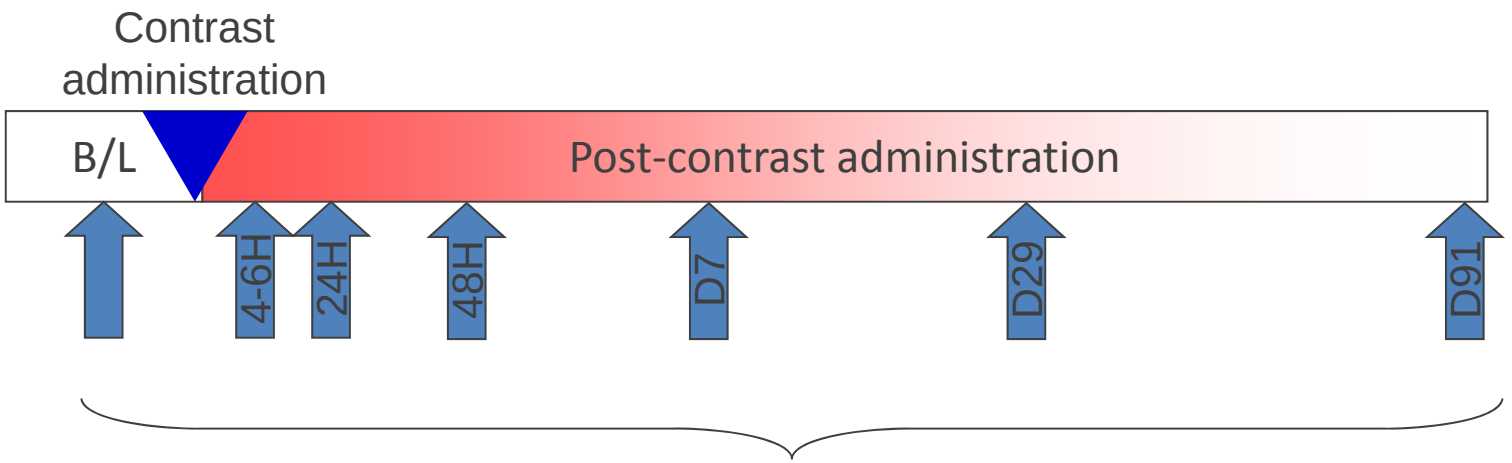
- **Group B**: Low-risk subjects: patients scheduled for contrast radiology study at low risk of developing CIN.
  N=20 patients

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

Ongoing study: anticipated completion 4Q2012

CIN Study Design

Patients scheduled to undergo contrast injection as part of planned radiological investigation



Urine & blood samples
(BUN/ s 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.
  - 1st sample taken at baseline before start of randomised treatment
  - 2nd sample taken 2 weeks post-cessation of randomised treatment (drug will have washed out by this time)
- Samples will be anaylsed 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