FDA-QUALIFIED KIDNEY TUBULAR INJURY COMPOSITE MEASURE

The FDA has approved the Qualification of the Composite Measure to identify the presence of drug-induced tubular injury in Phase I trials.

nexelis

disciplined agility

assay development ◦ specialty testing

The Composite Measure (CM) is calculated from the following biomarkers:

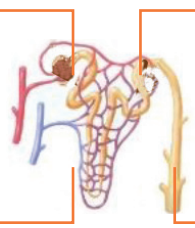
Urinary KIM-1, NGAL, cystatin C, osteopontin, clusterin & NAG

The CM determines the probability of tubular injury for a cohort treated by an investigated drug. All assay validations and clinical data for the CM were generated at Nexelis.

Composite Measure
- Clusterin
- Cystatin C
- KIM-1
- NGAL
- Osteopontin

Proximal Tubules
- KIM-1
- Clusterin
- NGAL
- Osteopontin
- Cystatin C

Loop of Henle
- Osteopontin



Distal Tubules
- Osteopontin
- Clusterin
- NGAL

Collecting Duct
- Cystatin C

We have assessed renal toxicity for over 40 drug programs since 2010

A dose cohort that exceeds the CM[1] threshold is potentially unsafe:

Composite Measure (CM) $CM = exp\{\sum_{i=1}^{11} log(CM_i)/m\}$			Subject (*i*) Composite Measure (CM_i) $CM_i = exp\{\sum_{j=1}^{6} \frac{1}{6} log(FC_{ij})\}$							
Visit Day	n	CM	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7	Subject 8
Predose	8	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
12h	7	1.15	NO CALC	1.19	1.22	1.31	1.07	1.08	1.08	1.08
24h	8	1.26	1.32	1.36	1.08	1.34	0.98	1.47	1.28	1.34
4 d	8	1.33	1.52	1.10	1.15	1.34	1.21	1.56	1.56	1.28
7 d	8	1.37	1.61	1.28	1.08	1.14	1.15	1.95	1.32	1.62
10 d	8	1.45	1.60	1.30	1.19	1.32	1.05	1.86	1.68	1.83
14 d	8	1.19	1.22	1.19	1.08	1.14	1.12	1.27	1.27	1.28
21 d	8	0.90	0.98	0.63	0.92	0.96	0.85	0.95	0.96	0.98
28 d	8	0.93	0.89	0.75	0.89	0.97	0.84	0.98	1.07	1.10

The subject CM_i at a given timepoint, *t*, is calculated from the fold-change (*FC*) from baseline for each biomarker (j) as defined above. Note that the log refers to the natural log transformation of the fold changes from baseline. The CM for the cohort (m) is derived at a given timepoint by calculated the geometric mean.

[1] CM User's Guide: https://fnih.org/sites/default/files/final/pdf/KSP-CompositeCOU-UserGuide-V1.1_20190515.pdf

OUR LEGACY

Over almost 30 years, Nexelis has maintained a "fit-for-purpose" assay development and validation philosophy.
This covers a range of ratification options, from feasibility to full validations using CAP, CLSI, or FDA bioanalytical guidelines that match the intended use.

Our validation procedures apply to novel biomarkers, proprietary technology transfers, and comprehensive bioanalytical services for biologics, where PK, ADA and immunogenicity assays are required.

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