A case study: Biomarker Analysis using Composite Measure (CM)

PP16

Introduction

In early phase clinical studies, it is critical to ensure safety of volunteers, particularly if the volunteers are healthy volunteers (HV), since HV have no prospect of benefit from participation in study. To mitigate risk to participants, researchers often attempt to maintain a sufficient safety margin to the dose/exposure at which renal toxicity was seen in animals; however, this may prevent development programs from evaluating doses/concentrations that are needed to achieve efficacy.

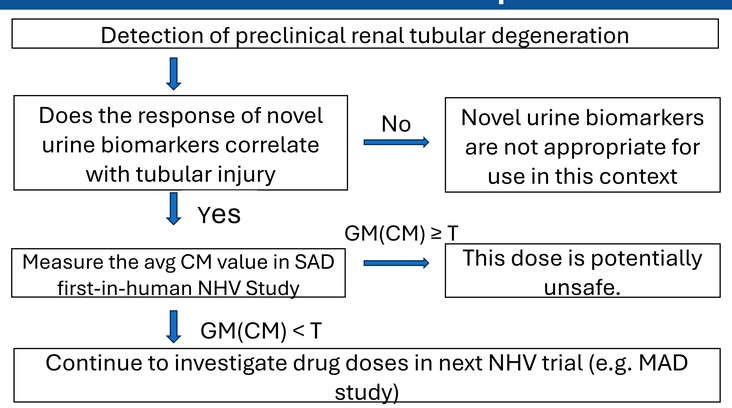
The current standard safety biomarkers have drawbacks and weaknesses in clinical trials. Currently, there are no biomarkers qualified by the FDA Biomarker Qualification Program to identify the presence of drug-induced renal injury in humans.

A biomarkers panel that may be more sensitive indicators of renal injury than current standard measures will aid in monitoring acute and sub-acute drug-induced tubular injury in clinical trials so that renal injury may be detected at an early and potentially reversible stage.

General Considerations:

- CM Method to be used in conjunction with traditional method.
- The table of CM threshold values provided were derived from a normal healthy volunteer (NHV) sample.
- The CM is likely to be more reliable in populations that closely mirror the population from which the CM was derived.
- Elevations in the CM may reflect a non-renal etiology, elevations of the CM should prompt further evaluation and investigation for renal as well as non-renal etiologies.
- The CM is not qualified for individual patient safety monitoring.

Decision Tree example



CM: Composite Measure; GM: Geometric Mean; T: Threshold

Methods

Single Arm New Cohort of Normal Healthy Volunteers

1.For each participant i and biomarker j where j = 1, 2,...., 6. ,
FCij = uCr-normalized fold-change from baseline for each biomarker.
uCr- normalized values is, ratio of concentration of biomarker to concentration of uCr at given timepoint

2.For each participant i, calculate the CM: $\boldsymbol{CM_i}$=exp $\left\{\sum_{j=1}^{6} \frac{1}{6} \log\left(\boldsymbol{FC_{ij}}\right)\right\}$

3.Calculate the geometric mean of the Composite Measure for the cohort of m participants: $\overline{\boldsymbol{CM}}$ =exp $\{\sum_{i=1}^{m} \log(\mathrm{CM}_i)/\mathrm{m}\}$

4. If $\overline{\boldsymbol{CM}}$ > T, this indicates that the new cohort of normal healthy volunteers is not consistent with the NHV data.

Single Arm: Threshold (T)					
n\P	50%	20%	10%	5%	1%
6	1.06	1.17	1.23	1.27	1.36
8	1.06	1.15	1.20	1.24	1.32
10	1.06	1.14	1.19	1.23	1.29
12	1.06	1.13	1.18	1.21	1.27
14	1.06	1.13	1.17	1.20	1.25
16	1.06	1.13	1.16	1.19	1.24
18	1.06	1.12	1.15	1.18	1.23
20	1.06	1.12	1.15	1.17	1.22

Two Arm New Cohort of Normal Healthy Volunteers

Using same steps as single arm, Calculate the ratio of the geometric means for the two cohorts: $GM_{ratio} = \overline{CM}_{Drug}/\overline{CM}_{Control}$
If GM_{ratio} > T this indicates that the new cohort of normal healthy volunteers is not consistent with the NHV data.

Case Study

In a Phase 1 trial one of primary endpoints is kidney safety composite measure biomarkers. Simulated data for 8 male participants was used to demonstrate the CM method to detect presence of kidney injury due to study drug. Data was collected at different timepoints, and summary results are shown in Table 1 while Results and conclusion in Table 2

Biomarker panel: Cluster in, Cystatin-C, Kidney Injury Molecule-1, N-acetyl-beta-D-glycosaminidase, Neutrophil Gelatinase-Associated Lipocalin, and osteopontin

Table 1. Summary Results

Participant	Post dose 1	Post dose 2	Post dose 3	Post dose 4
1001	1.5031	1.0978	0.7547	0.7317
1002	0.9228	0.4680	0.9455	0.9303
1003	0.7853	0.6407	0.7230	0.8517
1004	0.7864	0.8935	0.4597	0.7668
1005	1.4048	1.1458	0.6759	0.6715
1006	1.0180	0.5362	0.4700	0.5127
1007	1.3049	1.3565	0.9912	1.2097
1008	1.9057	1.0812	1.1692	1.0113
GeoMean (i.e. CM-bar)	**1.1494**	**0.8470**	**0.7373**	**0.8110**

Table 2. Results and Conclusion

(O≥T) <P%* in NHV	Time point	Post dose 1	Post dose 2	Post dose 3	Post dose 4
	T \ GM	1.1494	0.8470	0.7373	0.8110
P=50%	1.06	RTI	NRTI	NRTI	NRTI
P=20%	1.15	NRTI	NRTI	NRTI	NRTI
P=10%	1.20	NRTI	NRTI	NRTI	NRTI
P=5%	1.24	NRTI	NRTI	NRTI	NRTI
P=1%	1.32	NRTI	NRTI	NRTI	NRTI

O: Observed; T: Threshold; P: Probability

RTI: Renal Tubular Injury	*(GM CM >T)*
NRTI: No Renal Tubular Injury	*(GM CM <=T)*

Limitations

- CM threshold table is available only if sample size is between 6-20.
- The handling of missing data is not addressed
- Need to be used in conjunction with traditional measures

Summary

There are no evidence of any significant indication of the presence of Renal Tubular Injury (kidney injury) due to study drug for P value at 5%

References

Predictive Safety Testing Consortium Nephrotoxicity Working Group (YEAR) Executive Summary; Foundation for the National Institutes of Health. Available at: https://fnih.org/...

Pooja Puniya
Pooja.Puniya@parexel.com
Challa Venkata Harish
challa.venkataharish@parexel.com