The Implementation of the Analysis of a Partial Replicate Bioequivalence Study

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Summary:

We have programmed the analysis of a partial replicate bioequivalence study in SAS during the conduct phase of the study. We had previously reported such an implementation (Tanriverdio 2007), but this time the whole analysis was programmed according to CDISC SDTM and ADaM Standards and we will describe how we achieved to report the full analysis of the study within a few days after data base lock.

Statistical Background:

Two test formulations (T1 and T2) were to be compared against one reference formulation of Hydroxyurea. The aim is to demonstrate that the pharmacokinetic metrics AUC and Cmax of the test formulations are equivalent to those of the reference.

The efficient crossover design used 4 periods with administration of the reference treatment in two periods, and the resulting 4 treatment sequences were randomly allocated to the study subjects. The total sample size was 28 subjects to ensure 90% total power.

Methods:

The planning and implementation of the analysis was performed during the conduct phase of the study between Dec 2016 to Mar 2017. The programming of the pharmacokinetics was performed by the sponsor, the safety analysis was performed by a CRO. As this study design was new to medac, the whole analysis was programmed using the following steps:

1. Simulation of pharmacokinetic concentration-time profiles of each treatment in CDISC compliant format

2. Derivation of the pharmacokinetic metrics using a published SAS macro (Matos-Pita 2005).

3. Programming of listings, figures and descriptive statistics of the pharmacokinetic data

4. Statistical analysis of the bioequivalence metrics using a mixed model according to international guidelines.

Results:

The whole pharmacokinetic analysis was finalised and validated a few days prior to data base lock based on simulated data. After completion of the bioanalysis, the measured concentration data were transferred to the sponsor, and the programs were run and the results were checked.

The analysis included more than 500 pages, based on 7 Table templates, 5 Listing templates and 11 Figure templates. In particular the Figures were impressive to the study staff, as they combined both individual data and summary statistics.

The analysis confirmed the bioequivalence of both test formulations to the reference, the absence of period effects and the expected variability of the endpoints.

Conclusion:

The split of the analysis between sponsor and CRO was highly efficient, and lead to early result delivery for the key study objectives of bioequivalence.

References:

Tanriverdio F, Ring A. Planung und Implementierung der Auswertung einer replikativen Bioäquivalenzstudie mit Hilfe der „Scaled Average Bioequivalence“. KSFE 2007.

Matos-Pita AS, Lillo, BdM. Noncompartmental Pharmacokinetics and Bioequivalence Analysis. Pharmasug 2005, Paper SP07.