Special Topics

Helmut Schütz

AUC_{0-t} | Problem 1

What if

- The bioanalytical method was sensitive enough to measure *all* concentrations but a sample at the last time point (t_{last}) was missing (*e.g.*, vial broken in centrifugation)?
- The bioanalytical method was sensitive enough to measure *most* low concentrations but there were a few values at *t* below the LLOQ (lower limit of quantification)?

AUC_{0-t} | Problem 1

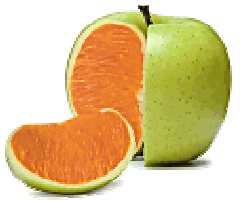
In BE we administer the same molar doses and assume constant inter-occasion clearances. Hence,

$$AUC_{0-t,T} = \frac{f_T \cdot D_T}{CL_T} \text{ and } AUC_{0-t,R} = \frac{f_R \cdot D_R}{CL_R}$$

with $D_T = D_R$ and $CL_T = CL_R$ we get $\frac{f_T}{f_R} = \frac{AUC_{0-t,T}}{AUC_{0-t,R}}$

- Example: t_{last} for one product is 24 h but due to missingness for the other one occasionally 16 h. If we follow guidelines blindly, the estimate will be biased because

$$\frac{f_T}{f_R} \neq \frac{AUC_{0-16,T}}{AUC_{0-24,R}}$$



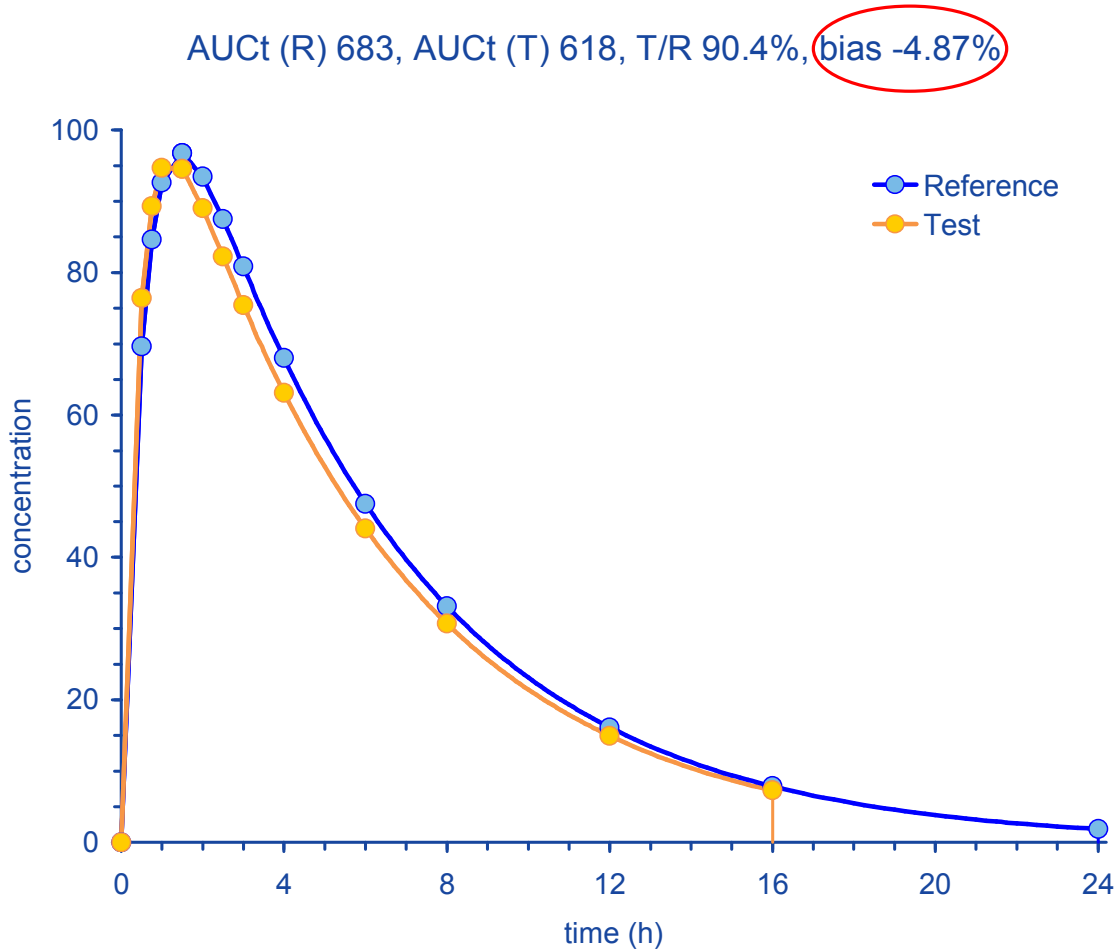
AUC_{0-t} | Problem 1

Only if the true relative BA-ratio is *exactly* 1, the chance to observe concentrations at t_{last} <LLOQ is similar for all treatments and the estimate will be unbiased

If the true BA-ratio is $\neq 1$, the estimate will be biased away from one (*i.e.*, the difference between treatments will be exaggerated)

- Regulators don't care because the patient's risk is not affected and the chance to demonstrate BE decreases
- Applicants should care since the producer's risk of failure increases

AUC_{0-t} | Problem 1



AUC_{0-t} | Solutions

Impute missings or BQLs by their estimates

- Requires reliable estimate of λ_z
- Implemented only in the current release of Phoenix/WinNonlin
- In other software or 'by hand' according to

$$C_t = e^{\log\left(\hat{C}_0\right)-\hat{\lambda}_z \cdot t}$$

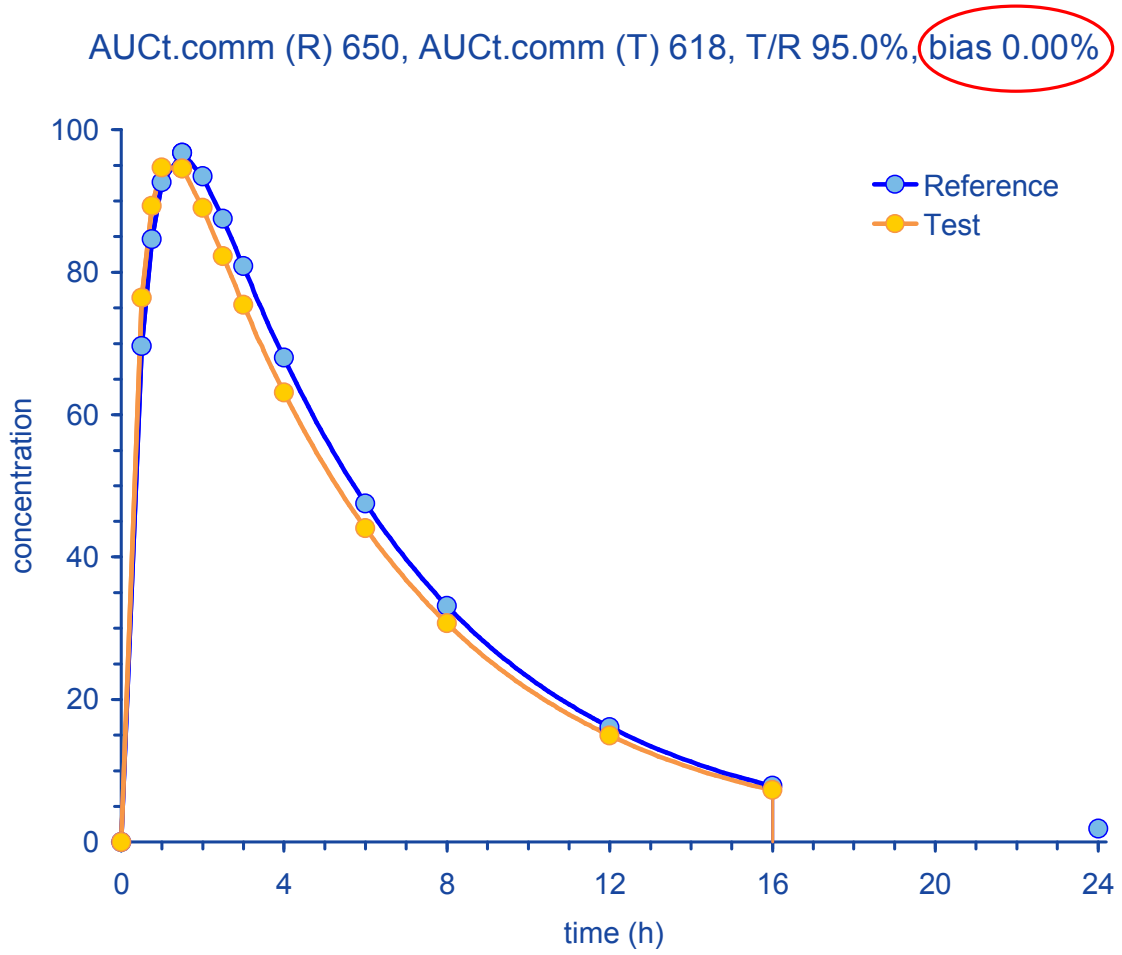
Compare *AUC*s in each subject where *both* treatments showed concentrations ≥LLOQ*

- Example: $t_{last,T}$ = 16 h, $t_{last,R}$ = 24 h, t_{last} *(Common)* = 16 h

$$\frac{f_T}{f_R} = \frac{AUC_{0-16,T}}{AUC_{0-16,R}}$$

* Fisher D, Kramer W, Burmeister Getz E. *Evaluation of a Scenario in Which Estimates of Bioequivalence Are Biased and a Proposed Solution: t_{last} (Common).* Clin Pharm. 2016;56(7):794–800. doi:10.1002/jcph.663. Open access.

AUC_{0-t} | Solution



AUC_{0-t} | Problem 2

What if

- a substantial number of samples in the late part of a profile is missing?
- Such a case might happen if a subject drops out from a study
- $AUC_{0-t(common)}$ will not necessarily help because according to most GLs a 'reliable estimate' of the extent of absorption is given if $AUC_{t-\infty}$ is ≤20% of $AUC_{0-\infty}$
- However, regulations ≠ science
  - For IR products ($k_a \gg k_e$) already at $2\times t_{max}$ absorption is practically complete (93.75%); at $4\times t_{max}$ 99.61% are already absorbed*
  - In the late part of the profile distribution / elimination prevails – which is drug-specific and not relevant for detecting differences between treatments

* Scheerans C, Derendorf H, Kloft C. *Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs.* Biopharm Drug Dispos. 2008;29(3):145–57. doi:10.1002/bdd.596.

AUC_{0-t} | Solution

EMA BE-GL Section 4.1.8 (2010)

- Subjects should not be excluded from the statistical analysis if $AUC_{(0-t)}$ covers less than 80% of $AUC_{(0-\infty)}$, but if the percentage is less than 80% in more than 20% of the observations then the validity of the study may need to be discussed.
  - For optimistic ones
    - Cross fingers and prepare for the discussion
  - For very brave ones
    - Give a justification in the protocol that absorption is already complete even at very early time points
    - Use $AUC_{0-t(common)}$
  - For brave ones
    - As above but state in the protocol a limit for the earliest acceptable truncation time; if earlier, exclude the subject from the comparison of *AUC*s

AUC_{0-t} | Solution

EMA BE-GL Section 4.1.8 (2010)

- For wary ones
  - Exclude the subject from the comparison of *AUC*s but – if C_{max} is well defined (*e.g.*, a couple of decreasing concentrations after t_{max}) – keep the subject in the comparison of C_{max}
  - Rationale
    - » In general the variability of C_{max} is substantially higher than the one of *AUC* and therefore, likely the study was powered for C_{max}
    - » Although power to show BE will slightly decrease for *AUC*, the overall power of the study will not be affected
- Prolonged (aka sustained) release formulations
  - By their biopharmaceutical design (flip-flop PK: $k_a \leq k_e$) the *late part* of the profile represents *absorption*
  - Exclude the subject from the comparison of *AUC*s

Special Case: Truncated AUC

Truncated *AUC* instead of AUC_{0-t} as the primary PK metric

- EMA
  - AUC_{0-72h} acceptable for all IR products
  - Stated as the method of choice in all product-specific guidances
  - *Not necessary* to extrapolate and show that 80% of $AUC_{0-\infty}$ are covered
  - Absorption is practically complete after $2–4\times t_{max}$
    - A truncation time of 72 hours is very conservative and based on the observation in clinicial studies that within three days any formulation has left the GIT
  - Problematic for controlled release products
    - $AUC_{0-\infty}$ is additionally required
    - A reliable estimate of λ_z is mandatory; might need longer sampling, since the late part of the profile represents absorption
    - However, once the formulation leaves the absorrption window (or the GIT) expect a rapid decrease in concentrations; don't use them to estimate λ_z

Dose Linearity and Proportionality

Various models exist

- The most simple one (dose proportionality) is employing conventional BE (90% CI) of dose-normalized PK metrics
  - Some authorities ask for a Bonferroni-adjustment due to the multiple tests
  - Comparing only two dose-levels cannot detect a deviation from dose proportionality

tests	α	$p_{\alpha=0.05}$	α_{adj}	% CI	$p_{\alpha,adj}$
1	0.050	5.00%	0.0500	90.00	5.00%
2	0.050	9.75%	0.0250	95.00	4.94%
3	0.050	14.26%	0.0167	96.67	4.92%
4	0.050	18.55%	0.0125	97.50	4.91%
5	0.050	22.62%	0.0100	98.00	4.90%

- For assessing dose linearity commonly the 'power-model' is used

$$E(Y \mid x) = a \cdot x^b$$

$$\log\left(E(Y \mid x)\right) = \log(a) + b \cdot \log(x)$$

where Y is a PK response (AUC, C_{max}), x the dose, $a > 0$, and $b \neq 0$

Dose Linearity and Proportionality

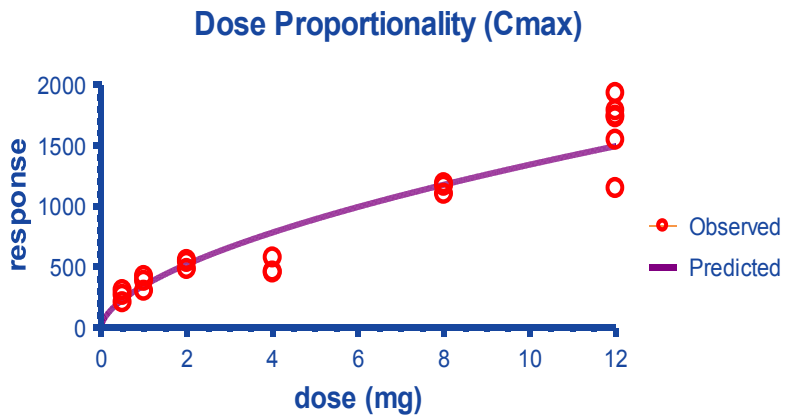
Various models exist

- 'Power-model'
  - The first form requires software for nonlinear regression
  - The second (linearized) form is a simple linear regression
  - The model is evaluated by examining the 95% confidence interval $[L, U]$ of the exponent b for departure from one
  - Decision criteria
    - if $0.75 < L < 1.0 < 1.25$ — no departure from dose linearity
    - if $1.0 < L < U < 1.25$ *or* $0.75 < L < U < 1.0$ — slight departure from dose linearity, but no practical significance from dose linearity
    - if $L > 1.25$ or $U < 0.75$ — reject hypothesis of dose linearity

Dose Linearity and Proportionality

Various models exist

- 'Power-model'
  - Example: FIM biological, six dose levels, C_{max}
    - *b* 0.587 (95% CI: 0.471 – 0.704)
    - CV 7.25%, correlation 0.9446
    - Since $U < 0.75$, deviation from dose linearity



Special Topics

Thank You!
Open Questions?

Helmut Schütz

BEBAC

Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria

helmut.schuetz@bebac.at