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Blinded Sample Size Review

Pros and Cons and beyond

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CHALLENGES FACED

- PK bioequivalence study = pivotal study in biosimilars development

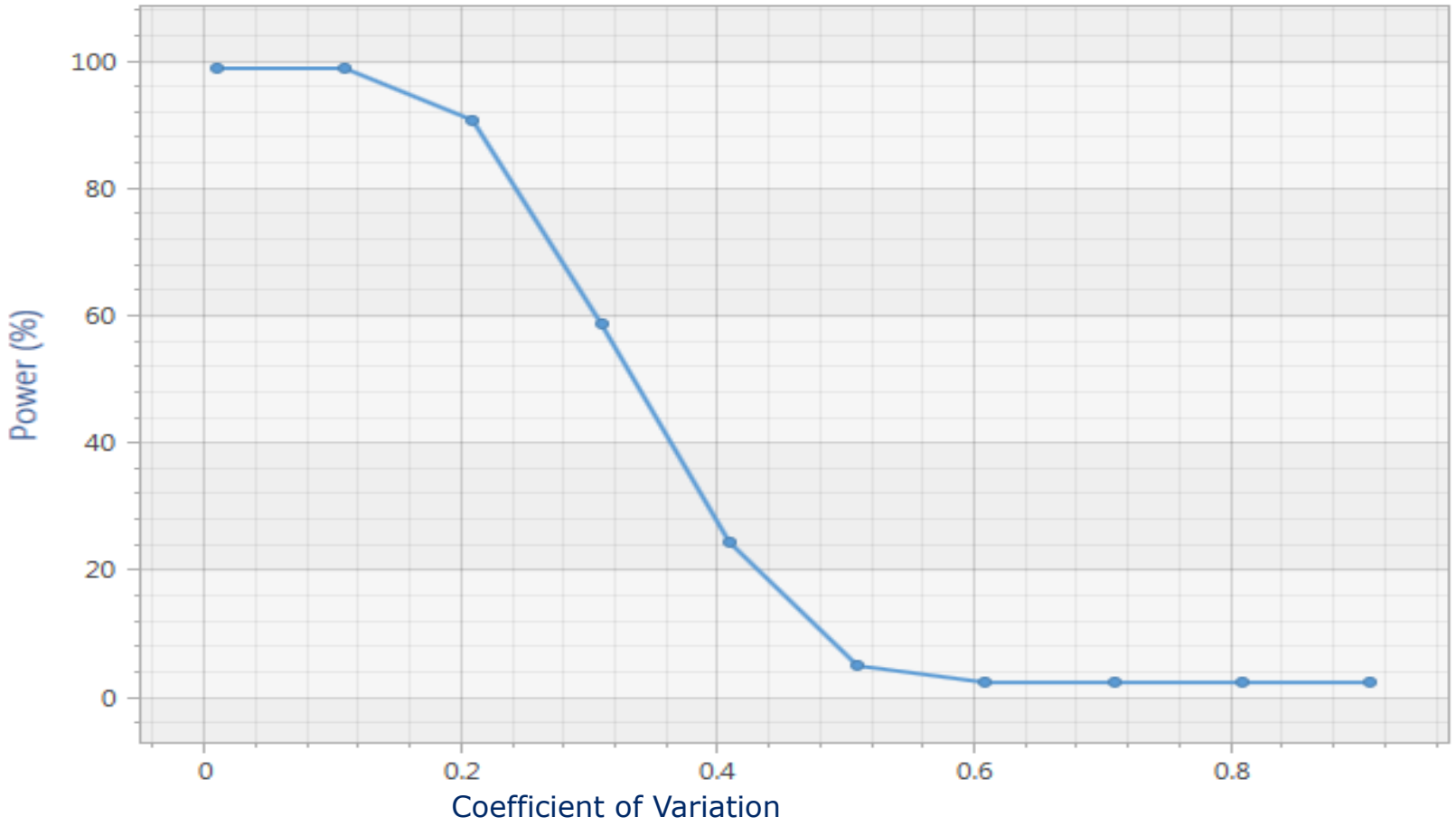
- Limited information on variability available in HV from originators studies
  - Small sample size
  - Only descriptive information (arithmetic mean) may be available
  - Estimates
  - Patient versus HV data

Parameter	30 µg/kg (n = 8)	60 µg/kg (n = 8)
C_{max}, ng/mL	43.6 (20.0)	104 (63)
t_{max}, h	8 (8-16)	12 (6-24)
$t_{½}$, h	50.9 (10.7)	62.1 (5.8)
$AUC_{[0-\infty]}$, ng·h/mL	887 (336)	3160 (2090)
CL/F, mL/h/kg	38.6 (15.4)	24.9 (12.1)

Data are presented as mean (SD), except for t_{max}, which is presented as median (range).

CHALLENGES FACED

- Example of power loss for cross-over BE study, as variability increases for fixed SS



N = 28
GMR = 0.95
EQM = [80; 125]

Blinded Sample Size Review

- Re-calculation of the sample size to achieve a pre-defined power level on the basis of the overall variability observed on blinded pooled data

- Leads to a re-estimation of the sample size up to a pre-defined maximum number of subjects to be enrolled (N_{max})

- Restricted designs (Wittes and Brittain, 1990):

  the final sample size ≥ the initially planned sample size:

$$N_f = \max(N_0, \min(\widehat{N}, N_{max}))$$

where N_0 is the initial SS, $\widehat{N}$ is the recalculated SS and N_{max} is the maximum SS

BSSR – limitations (1)

- Time needed to obtain required information to perform BSSR

- Recruitment of HV and single dose studies

=> all subjects dosed by the time the BSSR assessment is performed

- Relies on a biased estimate of the one sample variance (Kieser and Friede, 2003)

- Possible type I error rate inflation (Kieser and Friede, 2003) with non-inferiority and equivalence designs

BSSR – limitations (2)

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- Fiede and Kieser (2003) have derived a method for the analytical calculation of the type I error rate for Normally distributed data when the one-sample variance is used for sample size adjustment in non-inferiority and equivalence trials

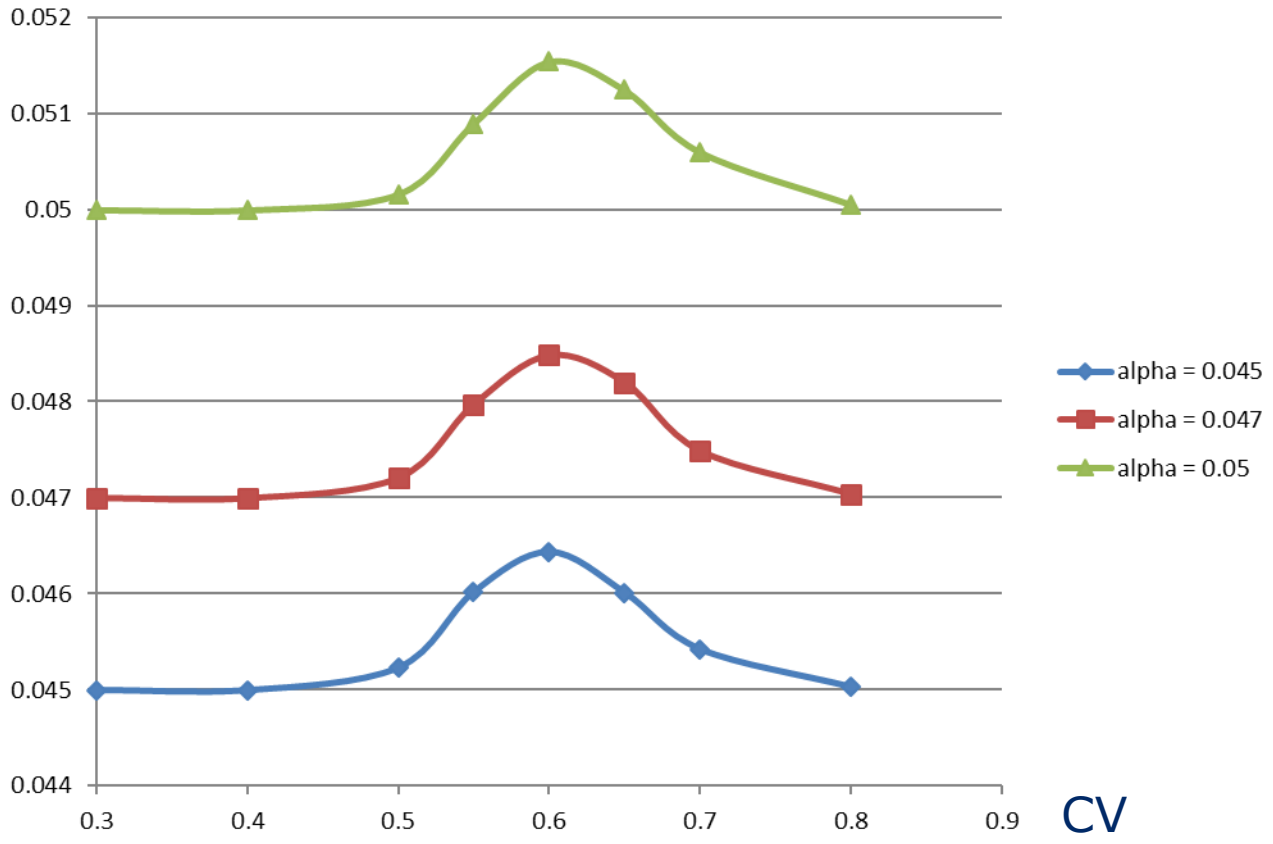
- Key idea is the decomposition of the test statistics T_i into components (Z_1, V_1, Z_2 and V_2^* or V_2) for which the joint density can be derived.

BSSR – limitations (3)

BSSR performed at 104 subjects out of 214 for a cross over design

Numerical integration results obtained using approx. SS formula and approx. density

Type I error rate



BSSR – Pros

- Small bias expected in the biosimilars development setting
- Possibility to use an adjusted alpha level
- With more than one PEP, inflation of the type I error rate is less «likely»
- Useful if large uncertainty about variability at the design stage to maintain the power of the study as initially planned

BSSR – example 1

Source / date available	geoCV (N)		
	Cmax	**AUCt**	**AUCinf**
Phase I planning assumption	33%		
BSSR		34%	
Final (EU Humira trt arm)	30.3 (79)	45.2 (79)	41.9 (77)
BI Phase I results (EU Humira trt arm)	30.4 (107)	33.5 (107)	38.5

BSSR – example 2

Assumed	Observed	Final
Protocol	BSSR	CSR
40% (max 50%)	>70%	N/A

BSSR – pause and think

- Log-normality assumption
- Influence of covariates
- Review of outliers
- Update of literature review

BSSR – Tips

- Use of «partial» data whenever possible/relevant
- Minimum sample size post BSSR to be set to avoid re-opening recruitment for a too limited benefit
- Carefull definition of maximum sample size – feasability to be factored in
- Updated literature review done in parallel
- Consideration of the route of administration

BSSR : Some references

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[1] Friede T, Kieser M. Blinded sample size re-assessment in non inferiority and equivalence trials. *Statistics in Medicine 2003*; 22: 995-1007.

[2] Wittes J, Brittain E. The role of internal pilot studies in increasing the efficiency of clinical trials. *Statistics in Medicine 1990; 9*: 65-72

[3] Elizabeth Hyland, Tim Mant, Pantelis Vlachos, Neil Attkins, Martin Ullmann, Sanjeev Roy and Volker Wagner (2016) Comparison of the pharmacokinetics, safety, and immunogenicity of MSB11022, a biosimilar of adalimumab, with Humira® in healthy subjects, Br J Clin Pharmacol.

[4] Christopher Wynne, Mario Altendorfer, Ivo Sonderegger, Lien Gheyle, Rod Ellis-Pegler, Susanne Buschke, Benjamin Lang, Deepak Assudani, Sandeep Athalye & Niklas Czeloth (2016) Bioequivalence, safety and immunogenicity of BI 695501, an adalimumab biosimilar candidate, compared with the reference biologic in a randomized, double-blind, active comparator phase I clinical study (VOLTAIRE®-PK) in healthy subjects, Expert Opinion on Investigational Drugs, 25:12, 1361-1370, DOI: 10.1080/13543784.2016.1255724

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THANK YOU

