Evaluation of designs for biosimilarity crossover trials analysed by nonlinear mixed effects models

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Context

- Similarity of different formulations of a biologic drug
  - ⇒ Pharmacokinetic (PK) bioequivalence crossover trials
    - Standard non compartmental analysis (NCA)[1,2]: at least 10 samples per subject
    - Nonlinear mixed effects models (NLMEM)[3,4]: fewer samples per subject
- Importance of choice of design in NLMEM
  - Balance between number of subjects and number of samples per subject
  - Choice of sampling times
  - Impact on study results (precision of parameter estimates, power of tests)
- Design evaluation and optimisation
  - Using the population Fisher information matrix
  - Extension to take account of within subject variability and discrete covariates changing between periods[5]
  - Implementation of these developments in PFIM 3.2[6]

Objective: to evaluate and apply the extension of the population Fisher information matrix for designing biosimilar crossover trials

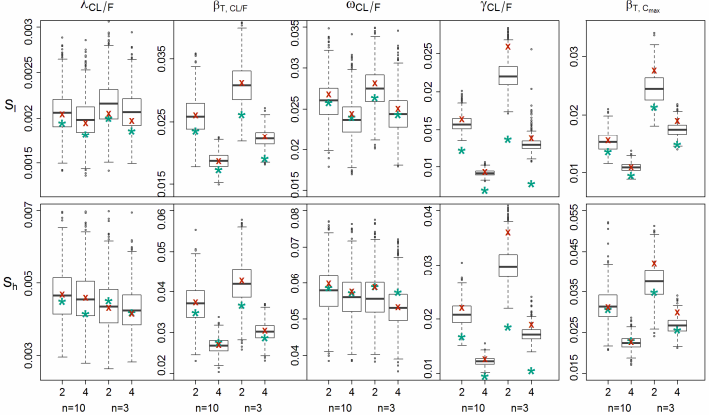
Methods

- NLMEM statistical model
  - Between (BSV, ω) and within subject (WSV, γ) variability
  - Treatment (β_T), period (β_P), and sequence (β_S) effects
- Bioequivalence Wald test
  - H_0: $\{ \beta_T \leq \log(0.8)$ or $\beta_T \geq \log(1.25) \}$
    - Rejection of H_0: $CI_{90\%}(\beta_T) \in [\log(0.8); \log(1.25)]$
- Simulation study
  - 1000 simulated crossover trials with 2 or 4 periods and 2 sequences
    - One-compartment model (parameters k_a, CL/F, V/F)
    - Designs with 40 subjects and n samples per subject and period
      - Asymptotic (A): n=10 and sparse (S): n=3
    - Treatment effect on CL/F and V/F: $\beta_{T,CL/F} = \beta_{T,V/F} = \log(0.8)$
      - ⇒ Due to the PK model: $\beta_{T,AUC} = \beta_{T,Cmax} = \log(0.8)$
    - Two levels of variability for random effects (residual error=10%)
      - S_l: BSV=10% for V/F and 20% for k_a and CL/F, WSV=BSV/2
      - S_h: BSV=50%, WSV=15%
  - Estimation using MONOLIX 2.4[7] for all simulated trials of each design
    - NLMEM parameters estimated by SAEM algorithm[8] and their standard error (SE_{est})
    - Computation of $\beta_{T,Cmax}$ and $SE_{est}(\beta_{T,Cmax})$ by delta method[9]
    - Empirical SE (SE_{emp}) : standard deviation of the 1000 parameter estimates
  - Prediction of the SE using PFIM 3.2 (SE_{pred}) for each design
    - Computation of $SE_{pred}(\beta_{T,Cmax})$ by delta method
    - ⇒ Comparison of SE_{pred} to the distribution of SE_{est} and to SE_{emp}
  - Predicted power of bioequivalence test under different H_1
    - Assuming $\exp(\beta_{T,CL/F}) = \exp(\beta_{T,V/F}) = \delta_1$ (⇒ $\exp(\beta_{T,AUC}) = \exp(\beta_{T,Cmax}) = \delta_1$) with δ_1=0.85, 0.9, 0.95, 1, 1.05 , 1.10 or 1.15

Results

- Evaluation of SE_{pred}

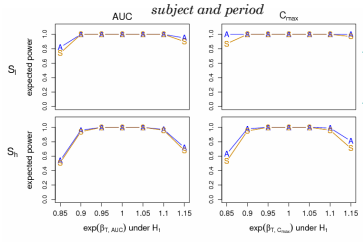
Boxplot of the 1000 SE_{est} for clearance parameters (mean value for reference: $\lambda_{CL/F}$, treatment effect: $\beta_{T,CL/F}$, BSV: $\omega_{CL/F}$ and WSV: $\gamma_{CL/F}$) and for the treatment effect on C_{max} ($\beta_{T,Cmax}$) estimated by delta method for crossover trials simulated with 2 or 4 periods, with 40 subjects and n=3 or 10 samples per subject and period. x: SE_{emp} ✱: SE_{pred}



  - SE_{pred} close to SE_{emp} for all fixed effects including β_T and for BSV
    - Similar results for k_a and V/F parameters (not shown)
  - SE_{pred} of WSV slightly underestimated even for 4-period trials
  - SE_{pred} of $\beta_{T,Cmax}$ also close to corresponding SE_{emp}

- Predicted power using PFIM 3.2

Predicted power of bioequivalence tests on $\beta_{T,AUC}$ and $\beta_{T,Cmax}$ for crossover trials simulated with 2 periods, 40 subjects and n=10 (asymptotic design, A) or n=3 (sparse design, S) samples per subject and period

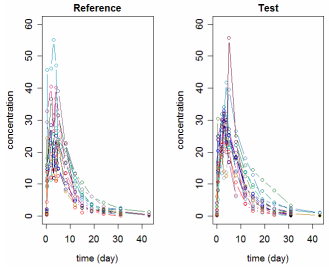


  - Similar results for asymptotic and sparse designs for $\delta_1 \in [0.95; 1.1]$
  - Lower power for δ_1=0.85 or 1.15 for S_h compared to S_l

Application

- Crossover trial comparing two formulations of a biologic drug in development at Novartis Pharma AG
  - 16 monkeys with 12 sampling times per period
- Parameter estimation by NCA
  - Concentrations below the limit of quantification (LOQ) deleted
  - Non zero residual concentration from first period at drug administration of second period considered as null
- NLMEM analysis using MONOLIX 3.1[7]
  - One-compartment model
  - Take acccount of residual concentrations of first period and LOQ
  - β_T, β_P and β_S + BSV + WSV on all PK parameters

Individual PK profiles for both formulations obtained from the crossover trial on monkeys



NLMEM parameters estimated by MONOLIX 3.1 using data from the crossover trial on monkeys

	λ_R	β_T	BSV	WSV
k_a	2.7 (1.0)	-0.35 (0.31)	0.44 (0.15)	0.78 (0.15)
V/F	5.8 10^{-2} (0.6 10^{-2})	-0.12 (0.08)	0.19 (0.06)	0.16 (0.05)
CL/F	6.63 10^{-3} (0.6 10^{-3})	-0.07 (0.07)	0.17 (0.05)	0.15 (0.04)
b	0.30 (0.01)	-	-	-

λ_R: mean PK parameters for reference period and sequence effects not reported

- Bioequivalence analysis by NCA and NLMEM
  - NCA: $\beta_{T,AUC}$ and $\beta_{T,Cmax}$ estimated by linear mixed effects model on the log-transformed parameters (AUC or C_{max})
  - NLMEM: $\beta_{T,AUC} = \beta_{T,CL/F}$ and $\beta_{T,Cmax}$ and its SE estimated by delta method

Bioequivalence analysis using NLMEM and NCA on data from the crossover trial on monkeys

	AUC		C_{max}	
	$\exp(\beta_T)$	$CI_{90\%}$	$\exp(\beta_T)$	$CI_{90\%}$
NLMEM	1.07	[0.96; 1.20]	1.07	[0.94; 1.22]
NCA	1.05	[0.92; 1.21]	1.07	[0.91; 1.26]

  - AUC and C_{max} bioequivalent by NLMEM
  - Only AUC bioequivalent by NCA

- Design optimisation using Fedorov Wynn algorithm
  - Crossover trial with 16 monkeys and 6 samples per monkey and period
  - Bioequivalence test on clearance (equivalent to test on AUC)
  - Parameter estimates of previous NLMEM analysis
    - Slight treatment effect: $\beta_{T,CL/F}$= -0.05
    - No period or sequence effect
    - Design taking into account WSV

Evaluation and optimisation of the design of the crossover trial on monkeys using PFIM 3.2

Design	Sampling times	Power	Number of subjects needed*	Number of samples needed*
Original	0.01, 0.33, 2, 3, 4, 5, 8, 12, 15, 19, 31, 43 days	0.9	16	384
Optimal	0.01, 2, 3, 4, 5, 31 days	0.85	19	228

** for a power of 0.9*

  - 16 monkeys to show PK similarity on CL/F by NLMEM using original design
  - Close results between original and optimal designs with 0.41 times less samples

Conclusion

- Evaluation of PFIM
  - SE_{pred} of treatment effect correctly predicted
    - ⇒ Computation of expected power and number of subjects needed
- Evaluation/optimisation of PK similarity trials analysed trough NLMEM
  - Requiring the knowledge of the model and its parameters
  - Allowing to reduce the number of samples per subject

⇒ PFIM: efficient tool for designing PK biosimilarity studies

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