Model-based bioequivalence analysis of recombinant human growth hormone using the SAEM algorithm: liquid or lyophilized formulation Omnitrope® versus original lyophilized formulation Genotropin®

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Context

- Standard bioequivalence analysis (FDA[1] and EMEA[2])
  - Compute AUC and C_{max} by non compartmental analysis (NCA)
  - Test on log parameters
    - Using linear mixed effects model with treatment, period, sequence, and subject effects
- Nonlinear mixed effects models (NLMEM)[3,4]
  - Simultaneous data analysis for all subjects

Objectives: mimick standard bioequivalence analysis using NLMEM and apply this method on a real dataset

Model-based Bioequivalence

- NLMEM bioequivalence analysis mimicking NCA analysis
  - Statistical model
    - Parametric pharmacokinetic (PK) model
    - Between and within subject variability
    - Treatment (β), period, and sequence effects
  - Parameter estimation by maximum likelihood
    - SAEM algorithm implemented in MONOLIX 2.4[5,6]
- Bioequivalence Wald test
  - Schuirmann's test[7] H_0: { $\beta \leq \log(0.8)$ or $\beta \geq \log(1.25)$ }
    - Rejection of H_0: $CI_{90\%}(\beta) \in [\log(0.8); \log(1.25)]$
    - $CI_{90\%}$ computed from the estimated treatment effect and its standard error (SE)
  - Wald test on secondary parameters[8]
    - $\beta_{AUC} = -\beta_{CL/F}$ (linear PK) → $SE(\beta_{AUC}) = SE(\beta_{CL/F})$
    - β_{Cmax}: nonlinear function of fixed effects → estimation of $SE(\beta_{Cmax})$ by delta method

Data

- Somatropin
  - Growth hormone (GH) of recombinant DNA origin
    - Use for GH deficiency in paediatrics and adults
  - Different drug formulations
    - Genotropin® by Pfizer: 5 mg/ml lyophilized formulation (reference)
    - Omnitrope® by Sandoz: 5 mg/ml lyophilized and 3.3 mg/ml liquid formulations (biosimilars)
- Randomized, double-blind crossover trial
  - 3 formulations, 3 periods, and 6 sequences
  - 36 healthy caucasian adults
    - 1 withdrawn subject, data only for the first period → analysis on 35 subjects
  - Dosing regimen: subcutaneous single dose of 5mg
  - Sampling times
    - 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours after each administration
  - Concentrations measured with LOQ=0.2 ng/ml
- Application
  - Complete data with 12 samples per subject and period
  - Sparsified data with 6 samples per subject and period
    - Design optimisation using PFIM 3.2[9,10]
      - Parameter estimates of Genotropin® data using NLMEM
      - Federov-Wynn algorithm

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[9] Bazzoli C et al. *Comput Methods Programs Biomed* . (2010)
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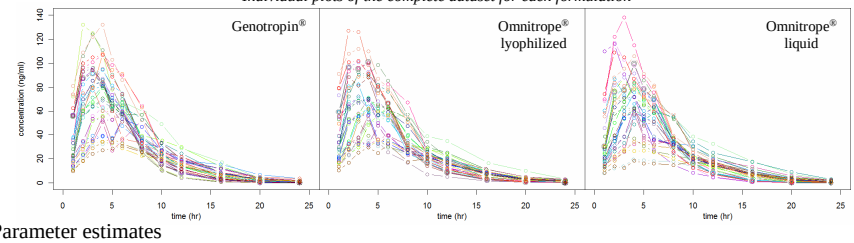
Results

- Model building
  - Structural model: one-compartment model with first-order absorption with a lag time and first-order elimination[11]
  - Statistical model
    - 40 fixed effects
      - Mean PK parameters for Genotropin® (λ)
    - 8 between (ω) and within subject (γ) variability parameters
    - Combined error model
    - Successful estimation for both datasets
- Complete data

Individual plots of the complete dataset for each formulation



  - Parameter estimates

Parameter estimates (SE) obtained by MONOLIX 2.4 for the complete data

	λ	$\beta_{lyophilized}$	β_{liquid}	ω	γ	a (ng/ml)	b
t_{lag} (h)	0.46 (0.08)	-0.25 (0.08)	-0.04 (0.06)	0.38 (0.06)	0.12 (0.06)	0.12 (0.02)	0.14 (0.004)
k_a (h^{-1})	0.32 (0.05)	-0.24 (0.1)	-0.11 (0.11)	0.15 (0.08)	0.27 (0.08)		
V/F (l)	25.83 (6.24)	-0.14 (0.12)	0.01 (0.13)	0.39 (0.04)	0.36 (0.04)	Period and sequence effects (28 parameters) not reported	
CL/F (h/l)	8.66 (0.86)	0.01 (0.03)	0.05 (0.03)	0.23 (0.01)	0.10 (0.01)		
$corr_{CL-V}$				0.95	0.67		

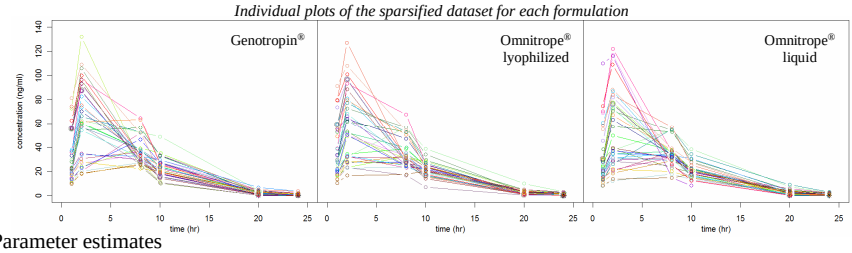
  - Bioequivalence analysis

Ratios and $CI_{90\%}$ obtained by NCA and NLMEM for AUC and C_{max} with the complete dataset

	AUC [$CI_{90\%}$]		C_{max} [$CI_{90\%}$]	
	NCA	NLMEM	NCA	NLMEM
Omnitrope® lyophilized vs. Genotropin®	0.99 [0.94; 1.03]	0.99 [0.95; 1.04]	0.92 [0.85; 0.99]	0.94 [0.84; 1.04]
Omnitrope® liquid vs. Genotropin®	0.95 [0.90; 0.99]	0.95 [0.92; 1.00]	0.90 [0.83;0.97]	0.92 [0.83; 1.02]

    - Similar ratios for AUC and C_{max} by NCA[12] and NLMEM
- Sparsified data
  - Sampling times: 1, 2, 8, 10, 20, 24 hours

Individual plots of the sparsified dataset for each formulation



  - Parameter estimates
    - Better fit with the proportional model error
  - Bioequivalence analysis

Ratios and $CI_{90\%}$ obtained by NLMEM for AUC and C_{max} with the sparsified dataset

	AUC [$CI_{90\%}$]	C_{max} [$CI_{90\%}$]
Omnitrope® lyophilized vs. Genotropin®	0.98 [0.94; 1.03]	0.87 [0.80; 0.95]
Omnitrope® liquid vs. Genotropin®	0.94 [0.89; 0.98]	0.89 [0.82; 0.97]

Conclusion

- Omnitrope® lyophilized and liquid bioequivalent to Genotropin® by NCA and NLMEM bioequivalence analysis
- Model-based bioequivalence test
  - Good statistical properties under asymptotic conditions
    - Correction needed for small sample size
  - Advantages compared to NCA
    - Few samples per subject → bioequivalence on patients, children
    - Nonlinear PK
    - Taking into account data below LOQ