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Bioequivalence study of a C1-esterase-inhibitor product (Cetor®) with optimised sampling design

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Introduction

Cetor is a highly purified C1-inhibitor concentrate prepared from human fresh frozen plasma and is used in the treatment of hereditary and acquired angioedema (HAE/AAE). Changes in the manufacturing process required a bioequivalence study to asses changes in PK.

Limitations:

- No healthy volunteers could be used
- Very small patient population

Aim:

- reduce the number of samples by trial simulation
- Establish bio-equivalency

Methods

1. PK model development

- Retrospective data
- 9 Patients, 4-9 samples per patient
- Total and functional protein assays
- Both data assessed simultaneously
- Estimation of fraction functional (F_{func})
- Endogenous production: zero-order infusion into the central compartment

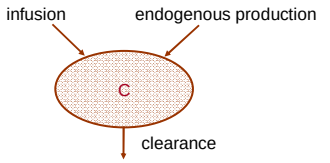

Figure 1. PK model

2. Evaluation of reduced sampling schedule

- By trial simulation
- Randomised crossover design, interval of 1 week between administration of products
- Two scenarios for PK characteristics of new product unequal:
  - (a) F_{func} is 25% lower
  - (b) CL is 20% higher
- 1000 trials for each scenario, n=10
- CPMP (n=14) & reduced (n=8) sampling design
- Assess power to detect a difference with a type I error of 0.05

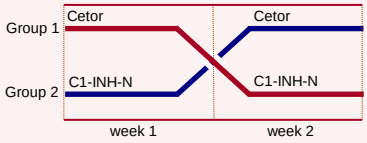

Figure 2. A Randomised cross-over design was used

3. Clinical trial

- Randomised, blinded, crossover
- n = 13 HAE patients
- Doses 1000U, 1500U and 2000U

Relative differences in PK properties induced by the adaptations in production process for CL, V, F_{func} estimated by introduction of a factor on the respective parameter:

$$CL = \theta_1 \cdot \theta_X^{PROD}$$
$$V = \theta_2 \cdot \theta_Y^{PROD}$$
$$F_{func} = \theta_1 \cdot \theta_Z^{PROD}$$

PROD=0 (Cetor) or PROD=1 (C1-INH-N)

The likelihood ratio test was used to test for significance ($p < 0.05$).

Results

1. PK model development

A one compartment model with linear clearance was shown to describe the data well. No improvement of fit could be established by adding compartments or introducing non-linear clearance.

Table 1. Parameter estimates from retrospective data

	Estimate	RSE
Cl	0.0676 L/hr	12.4%
V	4.41 L	5.96%
F_{func}	0.847	11.2%

2. Evaluation of reduced sampling schedule

Table 2. Results of trial simulations. Estimates of difference in parameter estimate and power of the design.

	Full design	Reduced design
F_{func} (75%)	76.9% (65.7-89.2)	75.6% (61.7-90.7)
Power	92.2% →	86.1%
CL (120%)	119% (98.6-140)	119% (97.8-147)
Power	47.8% →	40.3%

- Moderate reduction in power due to reduced schedule: -6.1 and -7.5% respectively.
- Power to detect differences in F_{func} was much higher than power to detect a difference in CL.

3. Clinical trial

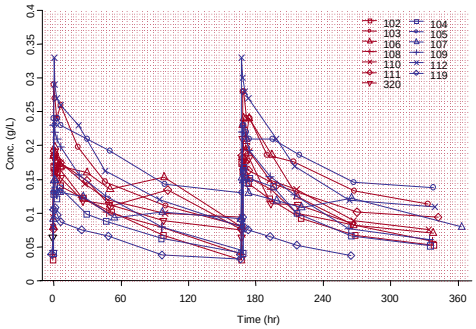

Figure 3. PK data for patients receiving Cetor (red) and C1-INH-N (blue) in the first week of treatment.

PK analysis:

- Interindividual variability for CL, V and F_{func} were 20.1%, 19.6% and 33.5% resp.
- IOV was significant on V (8.3%)
- No significant covariates were found

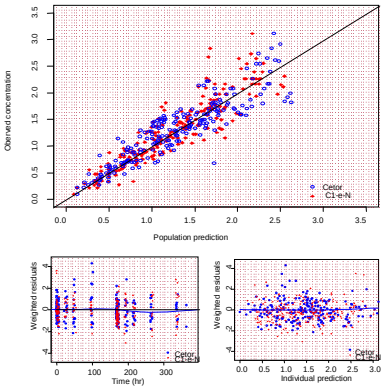

Figure 4. Goodness of fit plots: observed vs predicted (upper) concentrations, weighted residuals versus time (bottom-left), weighted residuals versus predicted concentrations (bottom-right)

Differences in PK parameters

No significant differences for the primary PK parameters were found since all 95% CI contained 1 (table 2). Furthermore, the 95% confidence intervals of the differences were all within the range of 80-125%.

Table 3. Differences in PK induced by the change in manufactering process.

	Mean ratio	95% conf. Interval
CL ($L.hr^{-1}$)	107%	93% - 123%
V ($kg.mL^{-1}$)	96%	88% - 107%
F_{func}	101%	92% - 110%

Discussion

- The power is only affected modestly by reduced sampling: the clinical trial was deployed using a reduced sampling design.
- EMEA guidelines state that 90% confidence intervals for the PK parameters should between 80-125% of the reference value. In this study, even the 95% CI were shown to be within these ranges and all contained 1.

Conclusion

- Trial-simulation were successfully used to assess whether a reduced sampling schedule could be used in a bioequivalence study of two C1-esterase-inhibitor products.
- The reduced sampling design only had minimal influence on the power of the study to find differences in PK.
- The results of the clinical trial showed that the adaptations in the production process did not lead to changes in PK parameters.