Population pharmacokinetic and pharmacodynamic analysis of tesamorelin in HIV-infected patients and healthy volunteers

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Objective

- To characterize the time course of growth hormone (GH) and insulin-like growth factor (IGF-1) concentrations, after subcutaneous administration of tesamorelin (Egrifta®), a synthetic analogue of growth hormone-releasing factor, in HIV-infected patients and healthy volunteers.

Methods

- A total of 41 patients receiving doses of 1 or 2 mg of tesamorelin daily during 14 consecutive days were included in this analysis.
- A previously developed population pharmacokinetic model of tesamorelin [1] was used as input function for the population pharmacokinetic and pharmacodynamics (PK/PD) models of GH and IGF-1.
- Indirect response models were used to describe the data and model parameters were estimated using NONMEM® 7.3.
- The effect of the selected covariates on the model parameters was also evaluated.
- The models were qualified using predictive checks.

Results

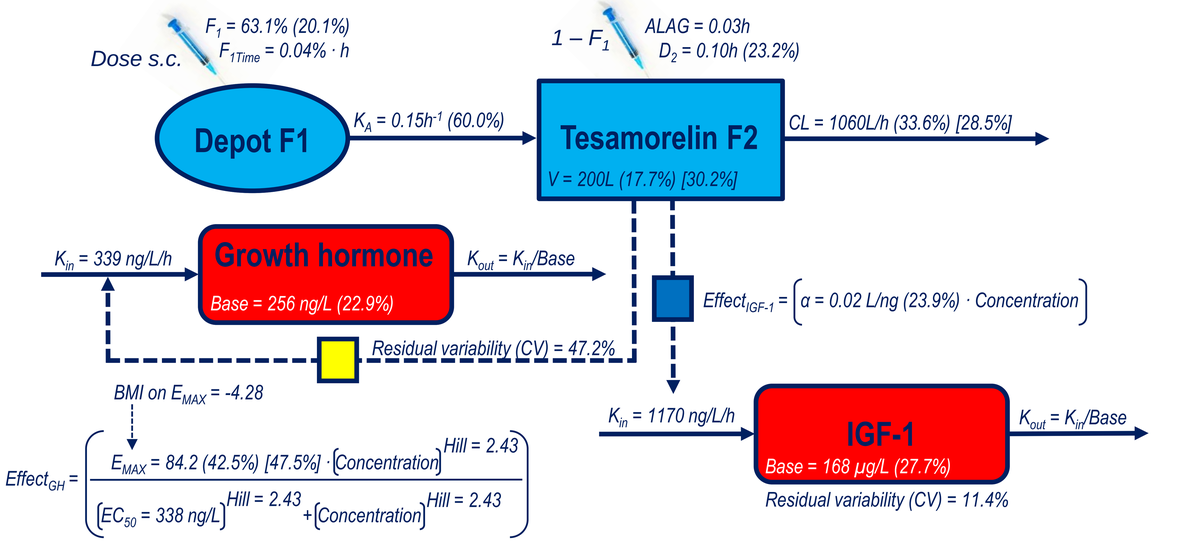

Figure 1. Schematic of the population pharmacokinetic and pharmacodynamic model for tesamorelin, growth hormone and IGF-1. *CL* represents typical value of clearance; *V* is the volume of distribution; K_a represents the first order absorption process; F_1 represents the fraction of tesamorelin absorbed by first order process. F_1 evolves with time and therefore, F_{1TIME} was defined as $F_{1TIME} = F_1 \cdot (1+\theta_x \cdot \text{TIME} - 0)$; *ALAG* represents the lag time after the zero order absorption process starts and D_2 represents the duration of the zero order input; k_{in} represents the zero-order rate constant for production of GH and IGF-1; k_{out} is the first-order rate constant for the loss of GH and IGF-1; *Base* represents the baseline values at steady state of GH and IGF-1; E_{MAX} represents the maximum effect; EC_{50} is the concentration that achieves half of maximum effect; *Concentration* represents concentration of tesamorelin; *Hill* is a parameter that determines the shape of the relationship. *BMI on* E_{MAX} represents the decrease on the effect when the body mass index (BMI) increases one unit. Parameters between () and [] represent interindividual and interoccassion variability, respectively.

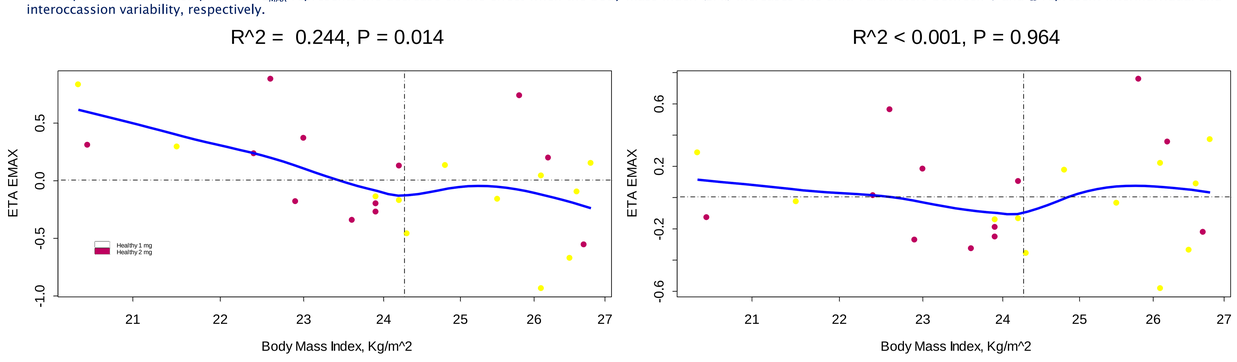

Figure 2. Scatterplot of the correlation between ETA E_{MAX} and body mass index for GH. Left panel represents the "preliminary" model and right panel represents the final model. The shrinkage values of ETA E_{MAX} were 17.5% (left panel) and 25.2% (right panel).

Reference : [1] Gonzalez-Sales M, et al. Clin Pharmacokinetics 2014 (*in press*).

Results (cont'd)

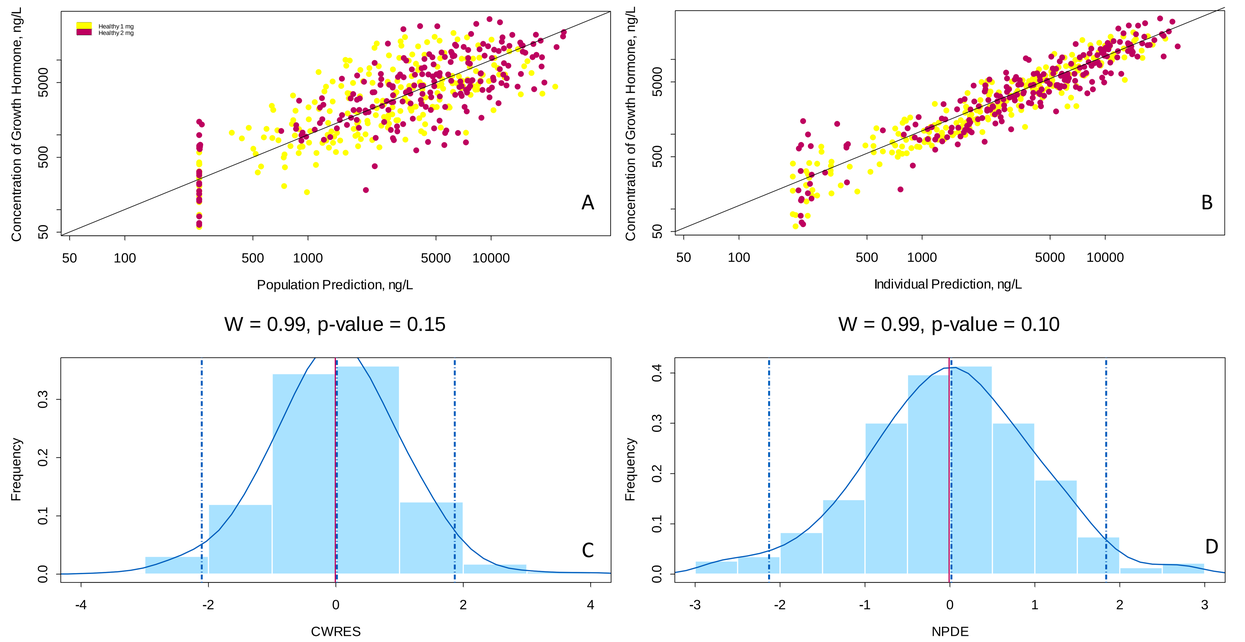

Figure 3. Diagnostic plots of the pharmacokinetic and pharmacodynamic model developed to characterize the time course of the growth hormone concentrations after tesamorelin administration. A) Observations vs population prediction; B) Observations vs individual predictions: C) Histogram of the conditional weighted residuals (CWRES) and D) histogram of the normalised prediction distribution errors (NPDE). For histograms, the normality test of Shapiro is provided. The mean of the NPDE was -0.010 (95 % CI -0.101, 0.079) and the value of the standard deviation was 0.996 (95 % CI 0.929, 1.053).

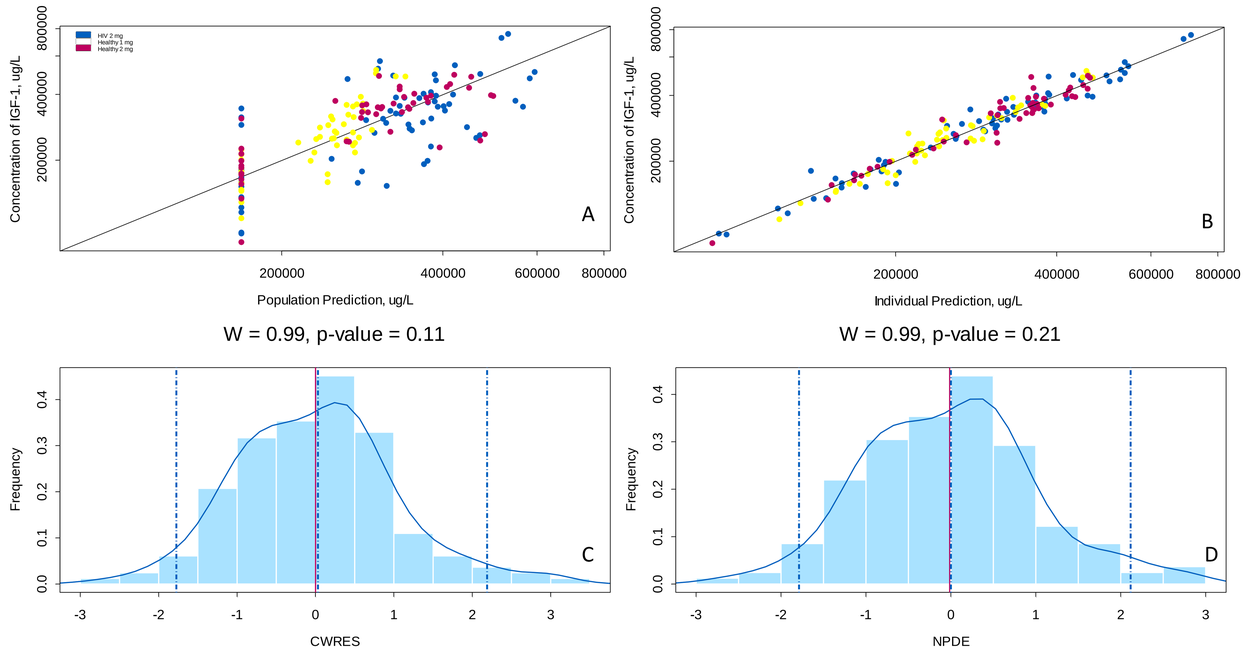

Figure 4. Diagnostic plots of the pharmacokinetic and pharmacodynamic model developed to characterize the time course of insulin-like growth factor 1 concentrations after tesamorelin administration. A) Observations vs population prediction; B) Observations vs individual predictions: C) Histogram of the conditional weighted residuals (CWRES) and D) histogram of the normalised prediction distribution errors (NPDE). For histograms, the normality test of Shapiro is provided. The mean of the NPDE was -0.002 (95 % CI -0.154, 0.155) and the value of the standard deviation was 0.987 (95 % CI 0.875, 1.086).

Conclusions

- ✓ The time courses of GH and IGF-1 concentrations following multiple doses of tesamorelin were well predicted by the PK/PD models developed using phase I data.
- ✓ Dose adjustment of tesamorelin based on BMI might be advisable.

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