Poster

# [P25-8] P25-8: Immunosuppressive drugs (3): Biomarkers and pharmacokinetics

Chair: Hideyuki Motohashi, Japan

Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall )

## [P25-8-7] Development of parametric and non-parametric population models and bayesian estimators for Envarsus tacrolimus formulation in liver transplantation

Jean-Baptiste Woillard[1], Jean Debord[2], Caroline Monchaud[3], Franck Saint-Marcoux[4], Pierre Marquet[5] (1.CHU Limoges, Univ Limoges, 2.CHU Limoges, Univ Limoges, 3.CHU Limoges, Univ Limoges, 4.CHU Limoges, Univ Limoges, 5.CHU Limoges, Univ Limoges)

Keywords: envarsus, tacrolimus, pharmacokinetics, parametric, non-parametric

### Background

Envarsus® is a new tacrolimus prolonged-release, once-daily formulation (Tac OD) recently developed by Veloxis (and marketed by Chiesi in Europe) using the patented technology Meltdose®. The objective of this work was to develop a population pharmacokinetics (popPK) model and an associated bayesian estimator (BE) based on a limited sampling strategy (LSS) for liver transplant patients treated with Envarsus®.

### Methods

One hundred thirteen full pharmacokinetics (PK) profiles (at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20 and 24h after dosing) were collected from 57 patients transplanted for up to 6 month and switched from Prograf® to Envarsus®. Data were split into a development (n=85 PK profiles) and a validation dataset (n=28 PK profiles). Modeling was performed using a parametric (ITSIM®) and a non-parametric method (Pmetrics®) in parallel. Covariates investigated were hematocrit, age, gender. The best LSS was determined using the newly developed MMopt algorithm (Bayard and Neely 2016). The BEs derived from the popPK models were evaluated using the validation dataset, by comparing the areas under the curve (AUCs) estimated using the full profiles with the AUCs estimated using the best three samples LSS.

### Results

The pharmacokinetics profiles were well fitted using a one compartment model with first order elimination, combined with two gamma functions to describe the absorption phase. None of the covariates studied significantly influenced the pharmacokinetics parameters. Both BEs combined with the 0, 8 and 12h LSS (=best LSS determined by MMopt) were characterized by an accurate estimation of Tac AUC in the validation dataset (ITSIM: relative bias±SD (RMSE)=0.89±7.32% (7.38%); Pmetrics: -2.62±8.65% (8.89%). The Wilcoxon test for paired samples showed no significant difference between the AUCs estimated using either techniques (p = 0.6272).

### Conclusions

The popPK models and BEs developed herein were able to predict adequately the exposure to the new Tac OD formulation in liver transplant patients and are now available on our ISBA website (www.pharmaco.chu-limoges.fr) while those developed with Pmetrics® can be provided for research purposes upon request. However, the LSS involved will require dried blood spot tacrolimus measurements to be used in practice.