**Impact of Concomitant Antiretrovirals, and CYP2C9 and CYP2C19 Polymorphisms on the Pharmacokinetics of Etravirine**

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**INTRODUCTION**

HIV type-1 (HIV) infected patients are routinely treated with combinations of three or four drugs (highly active antiretroviral therapy, HAART). Etravirine (ETR, TMC125) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated in combination with other antiretrovirals (ARV) for treatment-experienced patients of at least 6 years of age. A population PK model was previously developed using data from two phase III trials and pediatric trials. Despite the large variability in the ETR PK, only limited covariates could be identified to explain this variability. More recent data for ETR have become available, looking at specific concomitant ARV and polymorphisms of CYP2C9 and CYP2C19.

**OBJECTIVES**

The objectives of this analysis were:

- To develop a population PK model for ETR using data from studies TMC125-C206, TMC125-C216, TMC125-C238 and TMC125P0300 in adult treatment-experienced HIV-infected patients.
- To determine the influence of subject characteristics on the PK parameters of ETR, and possible drug interactions with other ARVs.
- To evaluate the final population PK model using simulation techniques.

**METHODS**

Data

A summary of the data used in the analysis is shown in Table 1. In study TMC125-C238, all subjects underwent rich PK sampling after 2 weeks of treatment, with sparse PK samples being taken at later visits. In studies TMC125-C206, -C216 and TMC125P0300, sparse PK samples were available for all subjects, and a richly sampled PK sub-study was performed in a small subset of the enrolled subjects.

**RESULTS**

A schematic overview of the model is shown in Figure 1. The model included between-subject variability (BSV) on CL/F, V/F and F, and with between-occasion variability (BOV) on F. Residual unexplained variability (EUV) was included in the model as a single proportional term, with 2 separate additive terms based upon study.

**DISCUSSION & CONCLUSION**

The model was able to describe the PK of ETR following oral administration of ETR at a dose of 200 mg BID with good precision and no bias.

WT and CRRL were included as covariates on CL/F, together with CYP2C9 and CYP2C19 phenotype. The exponent of 0.291 on weight was applied to pharmacologically important PK parameters in ETR. The model was able to describe the PK of ETR for adult subjects predominantly taking co-administered boosted protease inhibitors (PIs) as a background ARV regimen.

**REFERENCES**

2. Janssen R&D, Beerse, Belgium; Janssen R&D, Titusville, NJ, USA.

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**Table 3. Summary of Continuous Demographic Variables for all Studies (pooled)**

<table>
<thead>
<tr>
<th>N</th>
<th>Mean (%CV)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>817</td>
<td>44.6 (29.4)</td>
</tr>
<tr>
<td>WT (kg)</td>
<td>817</td>
<td>71.7 (21.4)</td>
</tr>
<tr>
<td>DLCL (cmeters)</td>
<td>817</td>
<td>104 (29.2)</td>
</tr>
</tbody>
</table>

**Analysis**

A base model was developed, which considered a previously developed model for ETR. Covariates were then evaluated to determine if they could add any of the variability in the PK of ETR. A mixture model was used to assign CYP2C9 and CYP2C19 phenotype for subjects where this information was not available. The analysis was performed using NONMEM (version 7.2 or higher) using the Full Information Maximum Likelihood (FIML) method to incorporate unobserved data using the POCH method with the Interaction option.

**All structural parameters were estimated with good precision, with a minor exception for the mixture model parameters due to the small number of subjects in the known PM group. The goodness-of-fit plots (Figure 2 and Figure 3) show minimal bias, although it can be seen that some individual observations were much lower than expected. This could have been due to a lack of compliance with medication intake on a few occasions.**

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**Figure 2. Goodness of Fit Plots of the Covariate Model**

A numerical predictive check was performed and indicated that approximately 5% of the observations were above and below the 5th and 95th percentiles of the prediction intervals, respectively.

**Figure 3. Conditional Weighted Residuals of the Covariate Model**

The model was able to describe the PK of ETR following oral administration of ETR at a dose of 200 mg BID with good precision and no bias.**