Introduction

- TMC125 (etravirine; ETR) is a next-generation NNRTI with potent activity against both wild-type HIV-1 and HIV-1 resistant to currently approved NNRTIs.
- Two phase III trials (DUET-1 and DUET-2) demonstrated significant antiretroviral benefit after 24 weeks of treatment with TMC125 in treatment-experienced patients with resistance to current NNRTIs. Except for a higher incidence of rash, patients treated with TMC125 had an adverse event (AE) profile similar to placebo.

Methods

- TMC125-C125 was a phase I, open-label, multiple dose PK trial in two stages, healthy HIV-1-negative volunteers matched by age, gender, and BMI.
- Volunteers with mild hepatic impairment (Child-Pugh, Class A) or moderate (Child-Pugh, Class B) hepatic impairment were enrolled.
- PK analyses were performed using WinNonLin Professional® 4.1 (Pharsight Corporation, Mountain View, CA, USA) and pharmacokinetic/pharmacodynamic analysis; PK and statistical analyses were performed using ProfessionalTM 4.1 (Pharsight Corporation, Mountain View, CA, USA) and their matched healthy controls were estimated with a linear mixed effects model.

Results

- A non-compartmental model with extravascular input was used for PK analysis. PK and statistical analyses were performed using WinNonLin Professional® 4.1 (Pharsight Corporation, Mountain View, CA, USA) and Microsoft Excel® (version 2000; Microsoft, Redmond, WA, USA).
- Descriptive statistics were calculated for the PK parameters of TMC125. Least squares mean (LSM) ratios for volunteers with hepatic impairment and their matched healthy controls were estimated with a linear mixed effects model. Primary TMC125 PK parameters on Day 1 and Day 8 were:
  - Cmax (ng/mL)
  - Cmin (ng/mL)
  - AUC0-12h (ng•h/mL)

- Safety and tolerability assessments (AEs; laboratory assessments; electrocardiograms; vital signs; physical examinations) were performed throughout the trial.
- Post-treatment safety visits took place 7 days and 31 ± 1 days after the last intake of trial medication.
- Severity and drug relationships of AEs to TMC125 were recorded.

Conclusions

- No clinically relevant difference in TMC125 PK was observed after administration in HIV-negative volunteers with and without hepatic impairment (mild/moderate).
- Short-term administration of TMC125 in HIV-negative volunteers with and without hepatic impairment was generally safe and well tolerated.
- TMC125 can be administered in patients with mild or moderate hepatic impairment without dose adjustment.

References

Pharmacokinetics of TMC125 in HIV-negative Volunteers with Mild or Moderate Hepatic Impairment

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1Tibotec Inc., Yardley, PA, USA; 2Tibotec BVBA, Mechelen, Belgium

Introduction

• TMC125 (etravirine, ETR) is a next-generation NNRTI with potent activity against both wild-type HIV-1 and HIV-1 resistant to currently approved NNRTIs.
• Two phase III trials (DUET-1 and DUET-2) demonstrated significant antiviral benefit after 24 weeks of treatment with TMC125 in treatment-experienced patients with resistance to current NNRTIs. Except for a higher incidence of rash, patients treated with TMC125 had an adverse event (AE) profile similar to placebo.
• TMC125 is mainly eliminated via the hepatobiliary route and is administered drugs.
• Enhanced liver toxicity and/or altered pharmacokinetics (PKs) of the administered drugs.
• To support administration of TMC125 in patients with hepatic impairment, a PK study in this population was conducted.

Methods

TMC125-C125 was a phase I, open-label, multiple dose PK trial in two sequential stages in HIV-negative volunteers with mild (Class A, Child-Pugh) or moderate (Class B, Child-Pugh) hepatic impairment (figure 1).

Table 1. Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild Impairment</th>
<th>Healthy</th>
<th>Moderate Impairment</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>57 (41–65)</td>
<td>56 (46–66)</td>
<td>54 (44–64)</td>
<td>51 (42–63)</td>
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<tr>
<td>Male, %</td>
<td>56 (2)</td>
<td>56 (2)</td>
<td>6 (17)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>81 (100)</td>
<td>81 (100)</td>
<td>81 (100)</td>
<td>81 (100)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171 (160–183)</td>
<td>172 (157–181)</td>
<td>174 (158–198)</td>
<td>175 (155–190)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74 (58–101)</td>
<td>72 (57–89)</td>
<td>79 (60–125)</td>
<td>82 (55–96)</td>
</tr>
</tbody>
</table>

Results

Safety and tolerability assessments (AEs, laboratory assessments, electrocardiograms; vital signs; physical examinations) were performed throughout the trial. Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication.

Conclusions

• No clinically relevant difference in TMC125 PK was observed after administration in HIV-negative volunteers with and without hepatic impairment (mild/moderate).
• Short-term administration of TMC125 in HIV-negative volunteers with and without hepatic impairment was generally safe and well tolerated.
• TMC125 can be administered in patients with mild or moderate hepatic impairment without dose adjustment.

References


Table 3. TMC125 PK parameters (mean ± SD) in volunteers with mild hepatic impairment

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Day 1</th>
<th>Day 8</th>
<th>Healthy</th>
<th>LS mean ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>467 ± 158</td>
<td>2903 ± 816</td>
<td>499 ± 149</td>
<td>0.92 (0.69–1.21)</td>
</tr>
<tr>
<td>AUC0–12h (ng•h/mL)</td>
<td>9546 ± 2630</td>
<td>10650 ± 1688</td>
<td>9546 ± 2630</td>
<td>0.87 (0.69–1.09)</td>
</tr>
</tbody>
</table>

Figure 2. TMC125 plasma PK profile in volunteers with mild hepatic impairment on Day 8.
Introduction

- TMC125 (etravirine; ETR) is a next-generation NNRTI with potent activity against both wild-type HIV-1 and HIV-1 resistant to currently approved NNRTIs.
- Two phase III trials (DUET-1 and DUET-2) demonstrated significant antiviral benefit after 24 weeks of treatment with TMC125 in treatment-experienced patients with resistance to current NNRTIs. Except for a higher incidence of rash, patients treated with TMC125 had an adverse event (AE) profile similar to placebo.
- TMC125 is mainly eliminated via the hepatobiliary route and is predominantly metabolized by the cytochrome P450 enzymes CYP3A4, CYP2C9 and CYP2C19, followed by glucuronidation. The drug itself is an inducer of CYP3A4 and an inhibitor of CYP2C9 and 2C19 (IC50 = 10.5 µg/mL [24.2µM]).
- Antiretroviral treatment in patients with hepatic impairment may lead to enhanced liver toxicity and/or altered pharmacokinetics (PK) of the administered drugs.
- To support administration of TMC125 in patients with hepatic impairment, a PK study in this population was conducted.

Methods

- TMC125-C125 was a phase I, open-label, multiple dose PK trial in two sequential stages in HIV-negative volunteers with mild (Class A, Child-Pugh score 5–6) or moderate (Class B, Child-Pugh score 7–9) hepatic impairment (figure 1).
- A non-compartmental model with extravascular input was used for PK analysis. PK and statistical analyses were performed using WinNonLin Professional® 4.1 (Pharsight Corporation, Mountain View, CA, USA) and Microsoft Excel® (version 2000; Microsoft, Redmond, WA, USA), and SAS® (version 9.1.3; SAS Institute Inc., Cary, NC, USA).
- Descriptive statistics were calculated for the PK parameters of TMC125.

Results

- Safety and tolerability assessments (AEs; laboratory assessments; electrocardiograms; vital signs; physical examinations) were performed throughout the trial.
- Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication.
- Severity and drug relationship of AEs to TMC125 were recorded.

Table 1. Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Panel A (Healthy)</th>
<th>Panel B (Mild Hepatic Impairment)</th>
<th>Panel B (Moderate Hepatic Impairment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57 (41–65)</td>
<td>56 (44–66)</td>
<td>54 (44–66)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>5 (62)</td>
<td>5 (62)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>8 (100)</td>
<td>8 (100)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171 (160–183)</td>
<td>172 (157–181)</td>
<td>174 (158–186)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74 (58–101)</td>
<td>72 (57–98)</td>
<td>79 (60–125)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 (20–32)</td>
<td>26 (20–32)</td>
<td>26 (22–32)</td>
</tr>
</tbody>
</table>

- A U C12h (ng•h/mL) = 2903 ± 816
- C max (ng/mL) = 1060 ± 268
- C min (ng/mL) = 499 ± 293

- One serious AE was reported. Tachyarrhythmia with cardiac failure was reported in one volunteer with moderate hepatic impairment and post-existing cardiomyopathy, which occurred 36 days after the last intake of TMC125.
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or the results of physical examinations.
- Grade 3 or 4 laboratory abnormalities were reported in one volunteer with mild hepatic impairment (hypercholesterolemia) and two volunteers with moderate hepatic impairment (low hemoglobin and hypophosphatemia in one, and increased lipase in another volunteer). Low hemoglobin was the only Grade 4 abnormality.

Conclusions

- No clinically relevant difference in TMC125 PK was observed after administration in HIV-negative volunteers with and without hepatic impairment (mild/moderate).
- Short-term administration of TMC125 in HIV-negative volunteers with and without hepatic impairment was generally safe and well tolerated.
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