Pharmacokinetics of TMC125 in once- and twice-daily regimens in HIV-1-negative volunteers

M Schöller-Gyure,¹ TN Kakuda,¹ G de Smedt,¹ B Woodfall,¹ R Lachaert,¹ G Beets,¹ M Peeters,¹ RM Hoetelmans¹
Tibotec BVBA, Mechelen, Belgium; ²Tibotec Inc., Yardley, USA

Introduction

TMC125 is a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI) with potent activity against both wild-type HIV-1 and viruses resistant to currently approved NNRTIs. The pharmacokinetics of TMC125 (Phase III formulation) administered in once- (qd) or twice-daily (bid) regimens, was evaluated in two Phase I trials C168 and C178.

Methods:
In these randomized crossover trials, TMC125 was administered following a meal for 7 days with a morning dose on Day 8. Dose regimens in trial C168 were 100mg bid and 200mg qd; in trial C178 200mg bid and 400mg qd. Pharmacokinetics of TMC125 were assessed on Day 1 and Day 8 over 12 or 24 hours. Pharmacokinetic (PK) parameters were calculated using noncompartmental methods. Safety and tolerability were assessed.

Results:
Twenty-four (23 males) and 41 (22 males) volunteers participated in C168 and C178, respectively. Day 8 PK results are shown below.

### C168

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>100mg bid (n=23)</th>
<th>200mg qd (n=24)</th>
<th>LS mean ratio qd/bid (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>215 ± 86</td>
<td>163 ± 76</td>
<td>0.74 ([0.69–0.80])</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>471 ± 147</td>
<td>659 ± 177</td>
<td>1.42 ([1.34–1.51])</td>
</tr>
<tr>
<td>AUC (0→24h)</td>
<td>2925 ± 1275</td>
<td>471 ± 2478</td>
<td>0.69 ([0.63–0.75])</td>
</tr>
</tbody>
</table>

### C178

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>200mg bid (n=23)</th>
<th>200mg qd (n=24)</th>
<th>LS mean ratio qd/bid (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>469 ± 141</td>
<td>364 ± 133</td>
<td>0.75 ([0.69–0.80])</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>3925 ± 1255</td>
<td>8054 ± 2748</td>
<td>1.05 ([1.00–1.07])</td>
</tr>
<tr>
<td>AUC (0→24h)</td>
<td>8195 ± 2428</td>
<td>17220 ± 5009</td>
<td>1.03 ([1.00–1.07])</td>
</tr>
</tbody>
</table>

Day 8 PK parameters (mean ± SD) (n=37) (n=24) (90% CI)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>TMC125 200mg bid</th>
<th>TMC125 100mg bid</th>
<th>TMC125 400mg qd</th>
<th>TMC125 200mg qd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>376 ± 161</td>
<td>344 ± 115</td>
<td>8195 ± 2428</td>
<td>17220 ± 5009</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>77 ± 25</td>
<td>77 ± 25</td>
<td>17220 ± 5009</td>
<td>17220 ± 5009</td>
</tr>
<tr>
<td>AUC (0→24h)</td>
<td>471 ± 2478</td>
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<td>17220 ± 5009</td>
<td>17220 ± 5009</td>
</tr>
</tbody>
</table>

### Study design

**Study design scheme and PK analyses**

- **Study design**: Both studies were Phase I randomised, crossover, multiple-dose PK trials in HIV-1-negative volunteers (C168) and C178, respectively.
- **Treatment**: TMC125 200mg bid or 400mg qd on Day 8 in the treatment arm was continued for a washout period of 14 days.
- **Dosing**: In C168, all volunteers received TMC125 200mg bid for 7 days and on Day 8 the dose was doubled to 400mg qd; in C178 400mg qd (bid) and 200mg qd (qd) for 7 days and on Day 8 200mg bid was administered.
- **AUC**: All doses were administered following a meal in both studies.
- **Safety and tolerability assessments**: Performance throughout the trial, food tolerance, safety, vital signs, laboratory tests, and physical examination.
- **PK parameters**: AUC, Cmax, Cmin.
- **Sample size**: 23 volunteers in C168 and 24 volunteers in C178.
- **PK parameter 200mg bid 400mg qd LS mean ratio qd/bid 12h (1.00–1.07)*
- **PK parameter 200mg bid 400mg qd LS mean ratio qd/bid 24h (1.37–1.50)*

### Conclusions

- **The daily systemic exposure to TMC125 obtained with qd administration is the same as that obtained by bid administration of an equivalent dose per day.**
- **The minimum plasma concentration of TMC125 is 25–26% lower with a qd regimen compared with a bid regimen of the same daily dose.**
- **The maximum plasma concentration is approximately 42–44% higher when given qd, compared with bid administration of the same daily dose.**
- **The pharmacokinetics of TMC125 in HIV-negative volunteers in the range of 200–400mg per day appear to be dose proportional.**
- **Short-term qd and bid administration of TMC125 in HIV-negative volunteers was generally safe and well tolerated.**
- **Further assessment of the efficacy and safety of TMC125 in a qd regimen is warranted.**

### References


### Acknowledgments

The authors would like to express their gratitude to the volunteers. We also acknowledge:
- MPI Bruelle, Sib & Pharmaceutical Research and Development, Irvine, USA
- Dossous Ph, MD, Asia Clinical Pharmacology Unit, Pitié-Salpêtrière, France
- SIB. France, MD, 505 115, Antwerpen, Belgium.