

Significant decrease in TMC125 exposures when co-administered with tipranavir (boosted with ritonavir) in healthy subjects

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Introduction

- TMC125 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that is being evaluated for the treatment of HIV-1 infected individuals.¹
- TMC125 has potent activity against both wild-type HIV and viruses resistant to currently approved NNRTIs.¹
- Tipranavir (TPV) is a recently approved non-peptidic protease inhibitor (PI) that is indicated for combination antiretroviral treatment of HIV-1 infected patients who are PI treatment experienced.²
- TPV is co-administered with ritonavir (RTV) to boost its pharmacokinetic parameters.
- In previous studies, it has been shown that RTV-boosted TPV (TPV/r) can be combined with the NNRTIs nevirapine and efavirenz without dose adjustment.²
- This study evaluated the steady-state pharmacokinetic interaction between TMC125 (formulation TF035) and TPV/r.

Methods

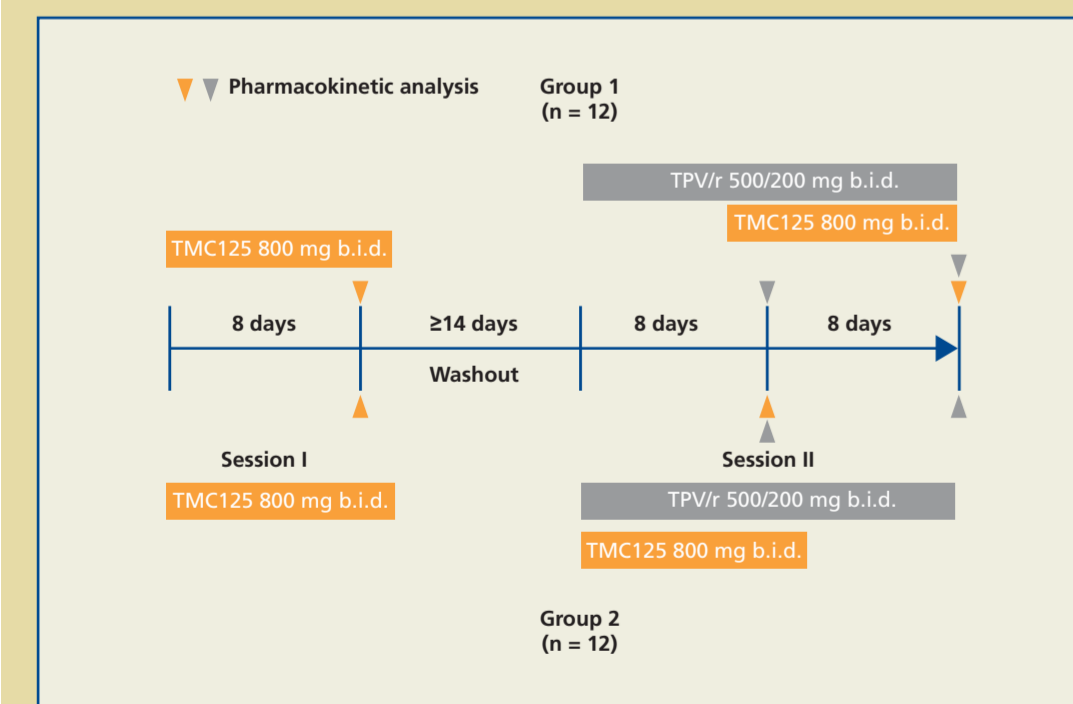
Study design

Study TMC125-C161 was a Phase I open-label, 2-way, crossover trial in which 24 healthy subjects were randomized to one of two groups as shown in Figure 1.

Each group participated in 2 sessions separated by a washout period of at least 14 days. Within each group, half the subjects were randomized to start with Session I and half were randomized to start with Session II.

All doses were taken within 15 minutes after a meal, the order of intake was RTV, TPV then TMC125.

Figure 1. Schematic of study design



Pharmacokinetic analysis

TMC125 and TPV/r pharmacokinetics were assessed at steady-state over 12 hours, as indicated in Figure 1. Plasma concentrations of TMC125, TPV and RTV were determined using validated liquid chromatographic-tandem mass spectrometry (LC-MS/MS) methods.

Pharmacokinetic and statistical pharmacokinetic analysis was performed using SAS System for Windows® version 8.2 (SAS Institute Inc., Cary NC 27512-8000, US). A non-compartmental model with extravascular input was used for the pharmacokinetic analysis.

Methods (continued)

Primary pharmacokinetic parameters measured included:

- C_{max} (ng/mL or µg/mL): maximum plasma concentration
- C_{min} (ng/mL or µg/mL): minimum plasma concentration
- AUC_{12h} (ng.h/mL or µg.h/mL): area under the plasma concentration-time curve from time of administration to 12 hours after dosing, calculated by linear trapezoidal summation.

Safety analysis

Adverse events (AEs) were monitored throughout the study period.

Severity and drug relationship of AEs towards TMC125 and TPV/r were recorded.

Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication.

Results

- Study population: 24 healthy subjects were randomized and received at least one dose of study treatment.
- Fifteen subjects completed the study.
- Nine subjects dropped out before trial completion, all due to AEs.
- The subject demographics are shown in Table 1.

Table 1. Demographic data

Demographic parameter	Group I N = 12	Group II N = 12	Total N = 24
Age, years – Median (range)	39.0 (19-55)	31.5 (23-54)	37.5 (19-55)
Height, cm – Median (range)	177.5 (165-192)	181.0 (156-194)	178.0 (156-194)
Weight, kg – Median (range)	80.5 (68-103)	73.5 (50-102)	78.5 (50-103)
BMI, kg/m ² – Median (range)	25.3 (19-30)	22.4 (19-30)	24.9 (19-30)
Gender, n (%)			
Male	10 (83.3)	9 (75.0)	19 (79.2)
Female	2 (16.7)	3 (25.0)	5 (20.8)
Ethnic origin, n (%)			
White/Caucasian	12 (100.0)	11 (91.7)	23 (95.8)
Oriental/Asian	0	1 (8.3)	1 (4.2)
Type smoker, n (%)			
Light smoker	5 (41.7)	3 (25.0)	8 (33.3)
Non smoker	7 (58.3)	9 (75.0)	16 (66.7)

Pharmacokinetic results

- The steady-state exposure (AUC_{12h}) of TMC125 was significantly reduced by 76% when the drug was co-administered with TPV/r compared to when given alone. (Table 2 and Figure 2a). No significant period or sequence effects were observed.
- TMC125 increased the steady-state exposure of TPV by 18% (Table 3 and Figure 2b).
- TMC125 significantly increased the steady-state exposure of RTV by 23% (Table 4 and Figure 2c).
- For TPV and RTV some significant period and/or sequence effects were observed. Considering the randomized and balanced study design and the pre-dose plasma concentrations demonstrating that steady state was reached after 1 week dosing, these effects were not considered to have major influence on the conclusions of the treatment comparison.

Table 2. Pharmacokinetic parameters for TMC125

Parameter	TMC125 alone (reference, n = 19) Mean ± S.D.	TMC125 + TPV/r (test, n = 19) Mean ± S.D.	Statistical analysis	
			LS mean ratio, % (test/reference)	90% CI, %
C_{max} , ng/mL	1263 ± 345	456 ± 307	29*	22–40
C_{min} , ng/mL	625 ± 227	183 ± 234	18*	13–25
AUC_{12h} , ng.h/mL	11236 ± 3210	3697 ± 3336	24*	18–33

pharmacokinetic data from Groups I and II are combined; *Level of significance: P ≤ 0.001; CI = confidence interval; LS mean = least square mean

Table 3. Pharmacokinetic parameters for TPV

Parameter	TPV/r alone (reference, n = 17) Mean ± S.D.	TPV/r + TMC125 (test, n = 19) Mean ± S.D.	Statistical analysis	
			LS mean ratio, % (test/reference)	90% CI, %
C_{max} , µg/mL	68.5 ± 22.5	77.8 ± 30.5	114	102–127
C_{min} , µg/mL	18.6 ± 10.4	25.5 ± 24.3	124	96–159
AUC_{12h} , µg.h/mL	503.1 ± 188.3	607.4 ± 329.1	118	103–136

pharmacokinetic data from Groups I and II are combined; CI = confidence interval; LS mean = least square mean

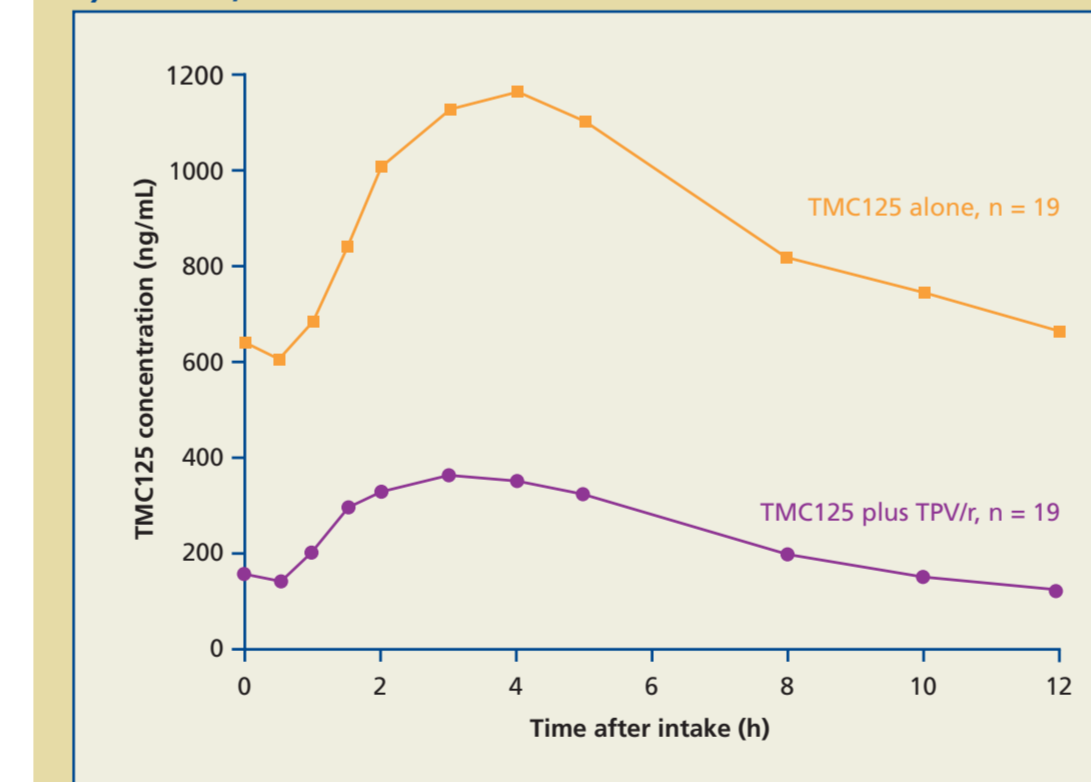
Table 4. Pharmacokinetic parameters for RTV

Parameter	TPV/r alone (reference, n = 17) Mean ± S.D.	TPV/r + TMC125 (test, n = 19) Mean ± S.D.	Statistical analysis	
			LS mean ratio, % (test/reference)	90% CI, %
C_{max} , ng/mL	1874 ± 861	2237 ± 1053	119*	104–137
C_{min} , ng/mL	84 ± 85	97 ± 87	134	87–208
AUC_{12h} , ng.h/mL	8542 ± 3952	10561 ± 5076	123*	105–145

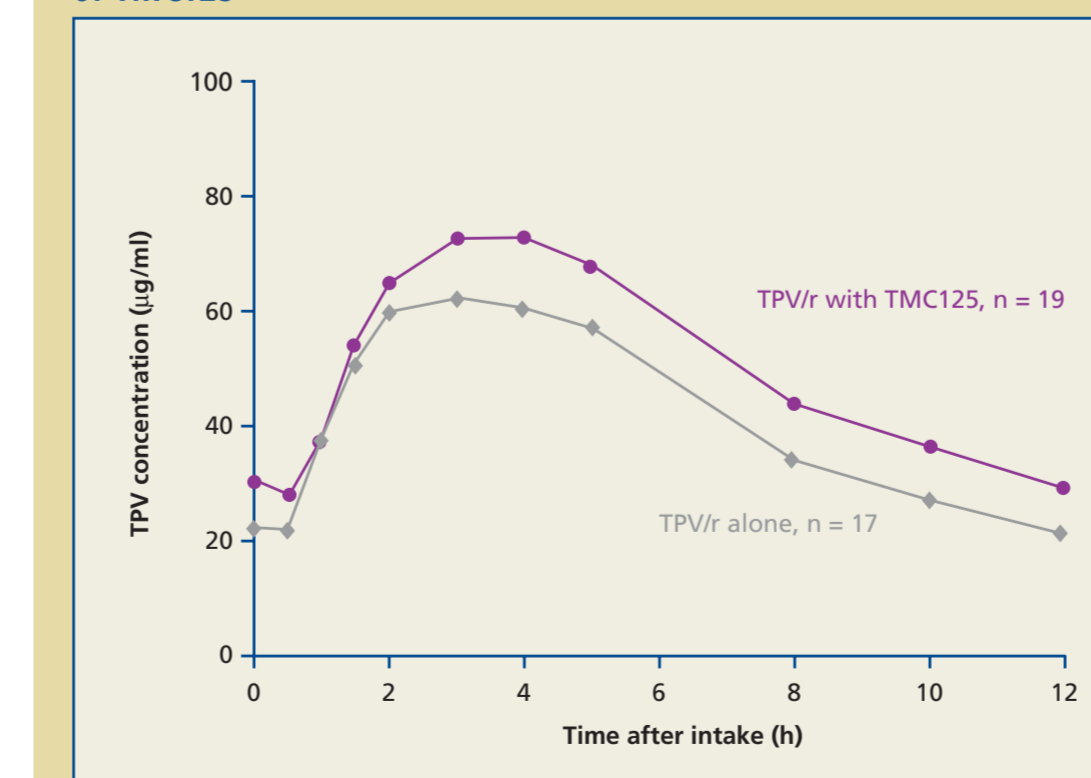
pharmacokinetic data from Groups I and II are combined; *Level of significance: P ≤ 0.05; CI = confidence interval; LS mean = least square mean

Figure 2. Mean steady-state plasma concentration-time curves.
 Note: pharmacokinetic data from Groups I and II are combined

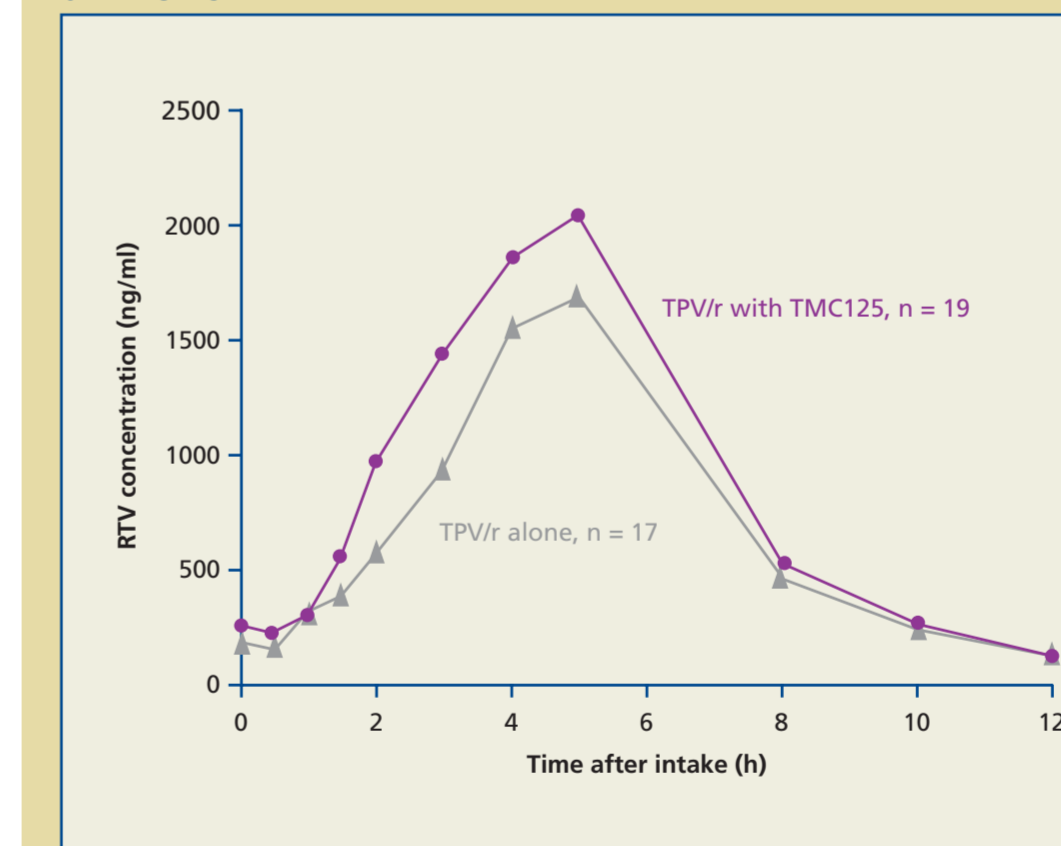
a) TMC125, with and without co-administration of TPV/r



b) TPV administered as TPV/r, with and without co-administration of TMC125



c) RTV administered as TPV/r, with and without co-administration of TMC125



Safety results

- No deaths or other serious adverse events were reported.
- No grade 4 adverse events were reported.
- Seven subjects experienced a grade 3 adverse event during the trial (ALT increase, n = 4; triglycerides n = 1 and one patient had a grade 3 ALT increase and a grade 2 maculopapular rash). All events occurred during the TPV/r or co-administration phase. In addition, one event was an increase in lipase which emerged during the follow-up. No grade 3 events were observed during the TMC125 (alone) treatment phase.
- Nine subjects (9/24, 38%) discontinued study treatments, six during the TPV/r treatment phase and three during the combination treatment phase. There were no discontinuations during the TMC125 (alone) treatment phase.

Results (continued)

- The most frequent reason for discontinuation was grade 3 laboratory abnormalities (ALT increase in 5 subjects and elevated triglycerides in one case). The remaining three subjects that discontinued study treatments reported a range of symptoms including grade 2 temperature increase, nausea, vomiting and headache.
- The overall incidence of AEs was lower in the TMC125 treatment phase than in the TPV/r and co-administration treatment phases (Table 5).
- Type and frequency of AEs in Group I subjects were generally comparable to those in Group II.
- The concomitant administration of TMC125 and TPV/r was generally safe.

Table 5. Safety summary

Safety	TMC125 N = 19	TPV/r N = 22	TMC125 + TPV/r N = 21	Whole Trial* N = 24
Most frequent adverse events (in >3 subjects over whole trial), n (%)				
Headache	4 (21.2)	4 (18.2)	5 (23.8)	13 (54.2)
Fatigue	2 (10.5)	7 (31.8)	4 (19.0)	9 (37.5)
Nausea	0	2 (9.1)	5 (23.8)	7 (29.2)
Pharyngolaryngeal pain	1 (5.3)	2 (9.1)	1 (4.8)	6 (25.0)
Vomiting	0	1 (4.5)	4 (19.0)	6 (25.0)
Flatulence	1 (5.3)	3 (13.6)	3 (14.3)	5 (20.8)
Loose stools	0	2 (9.1)	4 (19.0)	5 (20.8)
ALT increased	0	3 (13.6)	2 (9.5)	5 (20.8)
Nasopharyngitis	0	3 (13.6)	2 (9.5)	5 (20.8)
Dermatitis	0	0	2 (9.5)	4 (16.7)
n (%) with 1 or more AEs	8 (42.1)	16 (72.7)	18 (85.7)	23 (95.8)
n (%) of treatment stopped due to AEs	0	6 (27.3)	3 (14.3)	9 (37.5)
n (%) with 1 or more grade 3 AEs	0	4 (35.0)	2 (16.7)	7 (58.3)

Safety data from groups I and II are combined; N = number of subjects with data per treatment phase; n = number of subjects with that particular AE
 * Whole trial data: Successive events were counted only once; includes all treatment phases, screening, washout and follow-up.

Conclusions

- Due to the significant and clinically relevant decrease of TMC125 exposure, co-administration of TMC125 and TPV/r is not recommended.
- Exposure to TMC125 (expressed as AUC_{12h}) was decreased by 76% when combined with TPV/r (500/200mg b.i.d.).
- TPV and RTV exposures were increased by 18% and 23% respectively, when combined with 800mg TMC125 b.i.d. (formulation TF035).
- The pattern of AEs observed during co-administration of TMC125 and TPV/r is consistent with the safety profile of the individual drugs and is in line with the product description of TPV/r.

Acknowledgements

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 M-P. Bouche, J&J PRD, Beerse, Belgium

References

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