

# Pharmacokinetics (PK) and safety of adding TMC125 to stable regimens of saquinavir (SQV), lopinavir (LPV), ritonavir (RTV) and NRTIs in HIV+ adults

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## BACKGROUND

- TMC125 is an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI) with potent *in vitro* activity against both wild-type HIV and viruses resistant to currently approved NNRTIs.
- TMC125 is likely to be used in combination with ritonavir-boosted protease inhibitor (PIs), including dual boosted PI regimens.
- Lopinavir/ritonavir (LPV/RTV) and saquinavir (SQV) is a frequently-used dual boosted PI combination with well-characterized pharmacokinetics (PK).
- The PK interactions between TMC125 and these PIs need to be described before they can be used together safely and effectively in combination therapy.

## OBJECTIVES

- To evaluate the effect of TMC125 on PI concentrations in a dual boosted regimen of lopinavir/ritonavir (LPV/RTV) and saquinavir (SQV).
- To evaluate the effect of concomitant LPV/RTV and SQV on TMC125 concentrations, in comparison with historical controls.
- To assess the short-term safety and tolerability of co-administration of TMC125, LPV/RTV, SQV, and nucleoside reverse transcriptase inhibitors (NRTIs).

## METHODS

- Open label trial
- HIV+ adults with:
  - previously documented NNRTI resistance
  - VL <50 copies/mL for ≥8 weeks on a stable regimen comprising LPV/RTV, SQV, and 2 or more NRTIs
- TMC125 800 mg (formulation TF035) twice daily was added to the ongoing regimen for 2 weeks from Day 1 to Day 14
- Safety was assessed during the entire trial period, including 2 post-treatment follow-up visits at Days 21 and 44-46

## PHARMACOKINETIC (PK) METHODS

- 12-hour PK assessments were performed on Days -1 and 14, and pre-dose trough levels on Day 7
- Plasma concentrations of PIs and TMC125 were determined by validated LC-MS/MS methods
- PK analysis of PIs and TMC125 performed by noncompartmental PK methods
- PK parameters for LPV, SQV and RTV were analyzed using a linear mixed effect model
- TMC125 levels were descriptively compared with historical controls

## RESULTS

Table 1: Baseline Characteristics (N = 15)

Gender, n (%)	male 13 (87%), female 2 (13%)
Age*	46 years (36-63)
Height*	170 cm (162-183)
Weight*	65 kg (54-81)
Body mass index (BMI)*	22.5 kg/m <sup>2</sup> (20-29)
Ethnic origin, n (%)	Caucasian/white 11 (73%) Hispanic 3 (20%) Aboriginal/other 1 (7%)
CD4 cell count*	321/mm <sup>3</sup> (100-880)
CD4 cell fraction*	18% (4-42)
Duration HIV infection*	13 years (7-18)
HIV infection CDC stage A/B/C	5/5/5 (each 33.3%)

Table 2: Antiretroviral Regimens - PI doses

LPV/RTV/SQV BID doses (mg)	N
400/100/1000	6
400/100/800	5
400/200/800	1
533/133/800	3

Table 3: Antiretroviral Regimens - NRTIs

NRTI	N
lamivudine (3TC)	15
abacavir	10
didanosine	6
tenofovir	5
stavudine	3
zidovudine	2

The most common NRTI combination was abacavir + 3TC (n=6).

Figure 1: LPV Mean concentration-time curves on Day -1 and Day 14

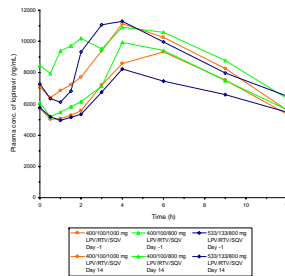


Figure 2: SQV Mean concentration-time curves on Day -1 and Day 14

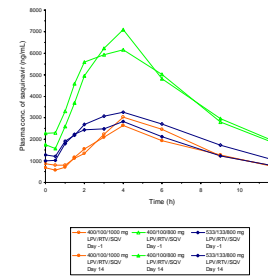


Figure 3: RTV Mean concentration-time curves on Day -1 and Day 14

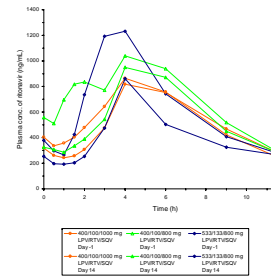
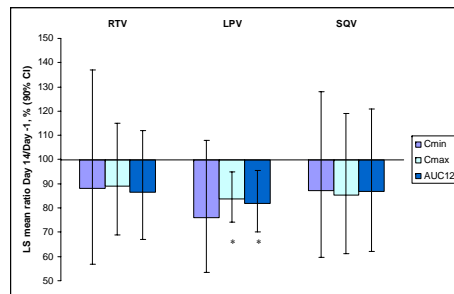
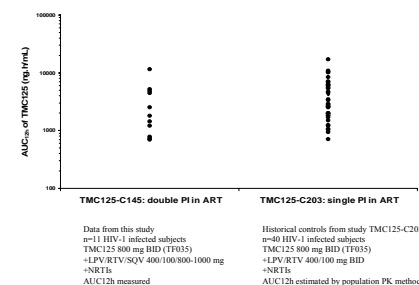


Figure 4: % change in PK parameters of PIs Day 14/Day-1 LPV/RTV/SQV 400/100/800-1000 mg (n=11)



\*P<0.05

Figure 5: PK of TMC125



## VIRAL LOAD (VL) RESULTS

- All patients had VL <50 copies/mL at screening
- All patients had VL <50 copies/mL at Day 14 (end of study treatment) and Day 44 (post-treatment follow-up)

## ADVERSE EVENTS (AE)

- All 15 patients completed the study
- No subjects discontinued TMC125 due to AE
- One subject experienced serious AE (meningitis and neurosyphilis) during the follow-up period
- 9/15 (60%) had at least 1 AE, mainly Grade 1 (mild)
- 6/15 (40%) had at least 1 AE that was possibly, probably, or very likely related to TMC125; all were Grade 1 (mild)
- Most common AE were diarrhea, burping, and fatigue (each n=2, 13%)
- No drug-related rashes or cardiac events were seen

## CONCLUSIONS

- TMC125 800 mg twice daily was generally safe and well-tolerated when given to HIV+ adults receiving stable regimens including LPV/RTV, SQV, and NRTIs.
- LPV C<sub>max</sub> and AUC<sub>12h</sub> were statistically significantly decreased, but LPV C<sub>min</sub> and PK parameters for RTV and SQV did not change significantly after 2 weeks co-administration with TMC125.
- The observed changes in plasma PI levels were of small magnitude (11-24%) and unlikely to be clinically significant.
- TMC125 PK results were comparable to those when co-administered with a single ritonavir-boosted PI (historical controls).

## REFERENCES

- Peeters, B, Woodfall, M, Schöller, J, Vingerhoets, E, Voorspoels, L, Bastiaens: 24-week primary analysis of TMC125-C203, a Phase IIb, randomized, controlled, double-blind trial to investigate the dose-response of TMC125 in 3-class-experienced HIV-1 infected patients. Tibotec, February 2004. Data on file.