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TMC125 in Combination With Medications Commonly Used in HIV Infection: Summary of Drug-Drug Interactions

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Introduction

- TMC125 (etravirine; ETR) is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with demonstrated activity in treatment-experienced HIV-infected patients, including those with NNRTI resistance[1,2]
- TMC125 is designed to have a high genetic barrier to the development of resistance[3,4]; TMC125 also maintains activity despite common NNRTI mutations[5,6]
- New formulation (F060) with improved bioavailability provides comparable exposure when dosed 200mg bid to the previous formulation (TF035) dosed 800mg bid
- Terminal half-life is 30 to 40 hours (distribution $t_{1/2}$ 3.9 to 5.4 hours)
- Exposure is reduced by 50% when administered in a fasted state. TMC125 should be administered following a meal[7]
- *In vitro*, TMC125 is a substrate and weak inducer of CYP3A4, a substrate and weak inhibitor of CYP2C9 and CYP2C19, and a weak inhibitor of P-glycoprotein (IC_{50} = 10.5 µg/mL [24.2µM])[8]
- Renal elimination is minimal (<1.2% of the administered dose)
- No drug interactions are anticipated with other drugs that are primarily renally excreted (eg, NRTIs and ribavirin)
- We summarize the pharmacokinetic (PK) interactions between TMC125 and other medications commonly used in HIV-infected patients

Methods

- Twenty-seven clinical drug-drug interaction studies have been conducted to date
- No effect boundary (clinical equivalence limit) for TMC125 is 50 to 200%, based on pharmacodynamics **(Figure 1)**[9]
- Steady-state PK studies include:
  - Two-way interaction studies with TMC125 and atorvastatin, clarithromycin, rifabutin, didanosine (ddI), tenofovir (TDF), elvitegravir/ritonavir (EVG/r), raltegravir (RAL), atazanavir (ATV), indinavir (IDV), and ritonavir-boosted (/r) protease inhibitors (PIs) ATV, darunavir (DRV), lopinavir (LPV), and tipranavir (TPV)
  - One-way effect of nevirapine (NVP), efavirenz (EFV), omeprazole (OME) and ranitidine (RAN) at steady-state on single-dose TMC125
  - One-way effect of steady-state TMC125 on steady-state fosamprenavir/r (FPV/r), LPV/saquinavir (SQV)/r, methadone, ethinyl estradiol/norethindrone, and single-dose sildenafil (SIL) and SQV
- Effect on PK parameters is presented as the LS mean ratio (90% CI)

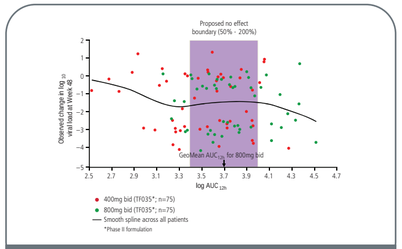

Figure 1. Relationship between TMC125 exposure (AUC_{12h}) and change in viral load at Week 48.

Results

- TMC125 had no clinically relevant effect on the exposure of co-administered drugs, except for the following **(Table 1)**:
  - TMC125 increased exposure to FPV (1.69), while decreasing exposure to sildenafil (0.43) and its active metabolite, N-desmethyl sildenafil (0.59)
  - Clarithromycin exposure decreased (0.61), but its active metabolite 14-OH-clarithromycin increased (1.21)
  - C_{min} of unboosted atazanavir decreased (0.53)
- TMC125 exposure was not affected to a clinically relevant extent upon co-administration, except for the following **(Table 1)**:
  - TMC125 exposure decreased when combined with TPV/r (0.24), NVP (0.45), or EFV (0.59)
- TMC125 PK were comparable to historical controls when co-administered with FPV/r, LPV/SQV/r, methadone, ethinyl estradiol/norethindrone, SIL or SQV
- Interactions of TMC125 with co-administered drugs are independent of formulation **(Table 2)**

Table 2. TMC125-C233: PK comparison with DRV/r and TDF between two TMC125 formulations

		LS mean ratios of AUC (90% CI)	
Dose regimen of co-administered drug	**Dose regimen of TMC125 (formulation)**	**TMC125**	**Co-administered drug**
DRV/r 600/100mg bid for 8 days	100mg bid for 16 days (F060)	0.63 (0.54–0.73)	1.06 (1.00–1.13)
DRV/r 600/100mg bid for 8 days	800mg bid for 16 days (TF035)	0.67 (0.52–0.86)	1.23 (1.16–1.31)
TDF 300mg qd for 8 days	200mg bid for 16 days (F060)	0.81 (0.75–0.88)	1.15 (1.09–1.21)
TDF 300mg qd for 8 days	800mg bid for 16 days (TF035)	0.68 (0.54–0.86)	1.16 (1.09–1.23)

Conclusions

- Drug interactions of TMC125 with medications commonly used in HIV therapy are well-characterized and manageable
- TMC125 can be combined with most of the drugs studied without dose adjustment:
  - Dose adjustments may be considered for FPV/r and sildenafil
  - TMC125 is not recommended in combination with other NNRTIs, TPV/r, full-dose ritonavir and unboosted PIs
  - Use of an alternative to clarithromycin is recommended when treating *Mycobacterium avium* complex
- TMC125 200mg bid (F060 formulation) is the dose used in the EAP and phase III trials:
  - Drug interactions are independent of formulation

References

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Table 1. PK interactions between TMC125 and co-administered drugs

	Dose regimen			PK parameters of co-administered drugs in the presence of TMC125					PK parameters of TMC125 in the presence of co-administered drugs					
						LS mean ratio* of PK parameters for co-administered drug (90% CI)					LS mean ratio† of PK parameters for TMC125 (90% CI)			
Co-administered drug	**Co-administered drug**	**TMC125**	**HIV status**	**N**	**PK**	**C_{max}**	**$AUC_{0,\ 12,\ 24h\ or\ last}$**	**C_{min}**	**N**	**PK**	**C_{max}**	**$AUC_{12h\ or\ last}$**	**C_{min}**	**Reference**
No dose adjustment necessary when co-administered														
Atazanavir/ritonavir	300/100mg qd for 7 days	800mg bid for 14 days (TF035)	–	13	↓	0.97 (0.89–1.05)	0.86 (0.79–0.93)	0.62 (0.55–0.71)	14	↑	1.30 (1.17–1.44)	1.30 (1.18–1.44)	1.26 (1.12–1.42)	Schöller-Gyüre M et al, HIV8 2006, abstract P278
Darunavir/ritonavir	600/100mg bid for 8 days	100mg bid for 16 days (F060)	–	13	↔	1.03 (0.98–1.09)	1.06 (1.00–1.13)	1.02 (0.89–1.17)	14	↓	0.68 (0.57–0.82)	0.63 (0.54–0.73)	0.51 (0.44–0.61)	Schöller-Gyüre M et al, Antiviral Ther 2007;12:789–796
Didanosine	400mg qd for 8 days	800mg bid for 16 days (TF035)	–	14	↔	0.91 (0.58–1.42)	0.99 (0.79–1.25)	NA	15	↔	1.16 (1.02–1.32)	1.11 (0.99–1.25)	1.05 (0.93–1.18)	Schöller-Gyüre M et al, IAS 2005, abstract WePe3.3C16
Ethinyl estradiol	0.035mg qd for 3 cycles	200mg bid for 15 days during 3rd cycle (F060)	–	16	↑	1.33 (1.21–1.46)	1.22 (1.13–1.31)	1.09 (1.01–1.18)	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, HIV8 2006, abstract P277
Norethindrone	1mg qd for 3 cycles	200mg bid for 15 days during 3rd cycle (F060)	–		↔	1.05 (0.98–1.12)	0.95 (0.90–0.99)	0.78 (0.68–0.90)	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, HIV8 2006, abstract P277
Lopinavir/ritonavir	400/100mg bid for 13 days and a single dose on Day 14	1,600mg bid for 13 days and a single dose on Day 14 (TF035)	–	13	↓	0.85 (0.62–1.05)	0.80 (0.49–1.07)	0.92 (0.15–1.68)	13	↑	1.15 (0.94–1.41)	1.17 (0.96–1.43)	1.23 (0.98–1.53)	Piscitelli SC et al, ICAAC 2002, abstract A-1824
Lopinavir	400mg bid	800mg bid for 14 days (TF035)	+	15	↓	0.84 (0.74–0.95)	0.82 (0.70–0.96)	0.76 (0.54–1.08)	NA	NA	NA	NA	NA	Harris M et al, CROI 2006, abstract 575b
Ritonavir	100mg bid ongoing regimen	800mg bid for 14 days (TF035)	+		↔	0.89 (0.69–1.15)	0.87 (0.67–1.12)	0.88 (0.57–1.37)	NA	NA	NA	NA	NA	Harris M et al, CROI 2006, abstract 575b
R-methadone	ongoing regimen	100mg bid for 14 days (F060)	–	16	↔	1.02 (0.96–1.09)	1.06 (0.99–1.13)	1.10 (1.02–1.19)	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, IAC 2006, abstract TuPe0084
S-methadone	ongoing regimen		–		↔	0.89 (0.82–0.96)	0.89 (0.82–0.96)	0.89 (0.81–0.98)	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, IAC 2006, abstract TuPe0084
Rifabutin	300mg qd for 14 days	800mg bid for 21 days (TF035)	–	12	↓	0.90 (0.78–1.03)	0.83 (0.75–0.94)	0.76 (0.66–0.87)	12	↓	0.63 (0.53–0.74)	0.63 (0.54–0.74)	0.65 (0.56–0.74)	Schöller-Gyüre M et al, IDSA 2006, abstract 1059
Tenofovir	300mg qd for 8 days	200mg bid for 16 days (F060)	–	19	↔	1.15 (1.04–1.27)	1.15 (1.09–1.21)	1.19 (1.13–1.26)	23	↓	0.81 (0.75–0.88)	0.81 (0.75–0.88)	0.82 (0.73–0.91)	Schöller-Gyüre M et al, ICAAC 2006, abstract A-371
Raltegravir	400mg bid for 4 days	200mg bid for 12 days (F060)	–	19	↓	0.89 (0.68–1.15)	0.90 (0.68–1.18)	0.66 (0.34–1.26)	19	↔	1.04 (0.97–1.12)	1.10 (1.03–1.16)	1.17 (1.10–1.26)	Anderson MS et al, IAS 2007, abstract TUPDB02
Elvitegravir/ritonavir	150/100mg qd for 10 days	200mg bid for 10 days (F060)	–	17	↔	1.07 (1.01–1.13)	1.06 (1.0–1.13)	1.06 (0.97–1.16)	34	↔	1.02 (0.86–1.20)	0.98 (0.88–1.08)	0.90 (0.83–0.97)	Ramanathan S et al, ICAAC 2007, abstract H-1407
Atorvastatin	40mg qd for 4 days	800mg bid for 11 days (TF035)	–	16	↓	1.04 (0.84–1.30)	0.63 (0.58–0.68)	NA	16	↔	0.97 (0.93–1.02)	1.02 (0.97–1.07)	1.10 (1.02–1.19)	Schöller-Gyüre M et al, IAS 2007, abstract WEPEA106
2-hydroxy-atorvastatin		800mg bid (TF035)	–	16	↑	1.76 (1.60–1.94)	1.27 (1.19–1.36)	NA	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, IAS 2007, abstract WEPEA106
Atorvastatin lactone		800mg bid (TF035)	–	16	↓	0.62 (0.56–0.69)	0.38 (0.34–0.42)	NA	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, IAS 2007, abstract WEPEA106
Saquinavir	800–1,000mg bid	800mg bid for 14 days (TF035)	+		↓	0.85 (0.61–1.19)	0.87 (0.62–1.21)	0.87 (0.60–1.28)	NA	NA	NA	NA	NA	Harris M et al, CROI 2006, abstract 575b
Omeprazole‖	40mg qd for 8 days	100 mg single dose (F060)	–	NA	NA	NA	NA	NA	18	↑	1.17 (0.96–1.43)	1.41 (1.22–1.62)	NA	Schöller-Gyüre M et al, IAC 2006, abstract TuPe0082
Ranitidine‖	150mg bid for 8 days	100 mg single dose (F060)	–	NA	NA	NA	NA	NA	18	↓	0.94 (0.75–1.14)	0.86 (0.76–0.97)	NA	Schöller-Gyüre M et al, IAC 2006, abstract TuPe0082
Dose adjustment may be necessary														
Clarithromycin§	500mg bid for 5 days	200mg bid for 8 days (F060)	–	15	↓	0.66 (0.57–0.77)	0.61 (0.53–0.69)	0.47 (0.38–0.57)	15	↑	1.46 (1.38–1.56)	1.42 (1.34–1.50)	1.46 (1.36–1.58)	Schöller-Gyüre M et al, IDSA 2006, abstract 1351
14-OH clarithromycin			–		↑	1. 33 (1.13–1.56)	1.21 (1.05–1.39)	1.05 (0.90–1.22)	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, IDSA 2006, abstract 1351
Fosamprenavir/ritonavir	700/100 mg bid ongoing regimen	800mg bid for 14 days (TF035)	+	8	↑	1.62 (1.47–1.79)	1.69 (1.53–1.86)	1.77 (1.39–2.25)	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, ICAAC 2006, abstract A-370
Sildenafil	50mg single dose	800mg bid for 13 days and a single dose on Day 14 (TF035)	–	15	↓	0.55 (0.40–0.75)	0.43 (0.36–0.51)	NA	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, IWCPHIV 2006, abstract 45
N-desmethyl sildenafil			–		↓	0.75 (0.59–0.96)	0.59 (0.51–0.68)	NA	NA	NA	NA	NA	NA	Schöller-Gyüre M et al, IWCPHIV 2006, abstract 45
Co-administration with TMC125 is not recommended														
Atazanavir	400mg qd for 7 days	800mg bid for 14 days (TF035)	–	14	↓	0.97 (0.73–1.29)	0.83 (0.63–1.09)	0.53 (0.38–0.73)	14	↑	1.47 (1.36–1.59)	1.50 (1.41–1.59)	1.58 (1.46–1.70)	Schöller-Gyüre M et al, HIV8 2006, abstract P278
Indinavir	800mg tid for 6 days	1,600mg bid for 14 days (TF034)	–	10	↓	0.72 (0.58–0.89)	0.54 (0.46–0.62)	0.24 (0.18–0.34)‡	10	↑	1.51 (1.16–1.97)	1.51 (1.20–1.90)	1.52 (1.20–1.91)	Baede P et al, ICAAC 2002, abstract A-1827
Saquinavir	1,200mg single dose	900mg bid 14 days (TF002)	–	12	↓	0.54 (0.34–0.86)	0.48 (0.29–0.80)	NA	NA	NA	NA	NA	NA	Baede P et al, ICAAC 2002, abstract A-1827
Tipranavir/ritonavir	500/200mg bid for 8 days	800mg bid for 16 days (TF035)	–	19	↑	1.14 (1.02–1.27)	1.18 (1.03–1.36)	1.24 (0.96–1.59)	19	↓	0.29 (0.22–0.40)	0.24 (0.18–0.33)	0.18 (0.13–0.25)	Schöller M et al, CROI 2006, abstract 583
Efavirenz	600mg qd for 14 days	900mg single dose (TF002)	–	NA	NA	NA	NA	NA	12	↓	0.83 (0.73–0.93)	0.59 (0.52–0.68)	NA	Baede P et al, ICAAC 2002, abstract A-1827
Nevirapine	200mg bid for 14 days	900mg single dose (TF002)	–	NA	NA	NA	NA	NA	5	↓	0.64¶	0.45¶	NA	Baede P et al, ICAAC 2002, abstract A-1827
Ritonavir	600mg bid for 7 days	400mg single dose (TF002)	–	NA	NA	NA	NA	NA	11	↓	0.68 (0.55–0.85)	0.54 (0.41–0.73)	NA	Baede P et al, ICAAC 2002, abstract A-1827

*Least squares mean ratio (co-administration with TMC125 versus co-administered drug alone); no effect = 1.00; †least squares mean ratio (co-administration with TMC125 versus TMC125 alone); ‡C_{trough}; NA = not available; §14-OH clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC) and therefore the overall activity against this pathogen may be altered. An alternative antibacterial (ie, azithromycin) is recommended for treatment of MAC when TMC125 is administered; ‖ranitidine and omeprazole were tested in the same volunteers but administered separately; ¶CIs not available due to limited sample size; reference definitions: CROI = Conference on Retroviruses and Other Infections; HIV8 = Eighth International Congress on Drug Therapy in HIV Infection; IAC = International AIDS Conference; IAS = International AIDS Society; ICAAC = Interscience Conference on Antimicrobial Agents and Chemotherapy; IDSA = Infectious Diseases Society of America Conference; IWCPHIV = International Workshop on Clinical Pharmacology of HIV Therapy

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