

Poster No. S3-7

TMC125 in Treatment-Experienced Patients: An Update

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Abstract

Background: TMC125, a next-generation NNRTI, has potent activity against both wild-type and NNRTI-resistant HIV-1.
Methods: Available data on TMC125 in treatment-experienced patients and drug-drug interaction data are reviewed.
Results: In an active control dose-finding study, TMC125 demonstrated significant and durable efficacy in treatment-experienced patients with NNRTI resistance. At 48 weeks, mean change in log₁₀ viral load (ITT, NC = F) at the selected dose of TMC125 was -1.01 versus -0.14 for control. At the same dose, 22% of patients on TMC125 achieved an undetectable viral load (88% of whom maintained to Week 48) versus 0% of controls. Data on the impact of NNRTI resistance-associated mutations on TMC125 fold change and outcome are evolving and confirm the *in vitro* virologic profile of TMC125. Favorable safety and tolerability for TMC125 have been demonstrated in a placebo-controlled, double-blinded trial. The most common adverse events (AEs) were diarrhea, abdominal pain, nausea, headache, and rash. Only rash was numerically more frequent with TMC125 than with placebo and was generally mild to moderate with infrequent discontinuations. No frequent or consistent neuropsychiatric AEs were reported compared with placebo. Extensive drug-drug interaction data with TMC125 indicate it can be co-administered without dose adjustment with most medications commonly used in HIV-infected patients.
Conclusion: TMC125 is the first NNRTI to demonstrate significant and durable efficacy in treatment-experienced patients with NNRTI resistance, with a favorable safety and tolerability profile. TMC125 can be combined with most medications without dose adjustment. The DUET registration trials are ongoing in treatment-experienced patients.

Introduction

- The clinical utility of currently-approved NNRTIs is limited by essentially complete cross-resistance within the class after development of resistance to one NNRTI
 - Transmitted NNRTI resistance also leads to a high rate of failure of an initial NNRTI-based HAART regimen¹
- There is an unmet medical need to expand the NNRTI class to those patients whose virus is resistant to current NNRTIs
- TMC125 (etravirine; ETR), a next generation NNRTI, is highly active *in vitro* against both wild-type and NNRTI-resistant HIV-1 strains and has a high genetic barrier to the development of resistance *in vitro*.³
 - TMC125 is active against HIV-1 with single and double NNRTI-resistance mutations: K103N, Y181C, K103N+Y181C
 - TMC125 has high potency against NNRTI-resistant clinical isolates (EC₅₀ <10 nM for >80% of approximately 2,000 NNRTI-resistant clinical isolates)
- TMC125 has demonstrated good tolerability as well as significant antiviral activity in treatment-experienced patients who were resistant to other NNRTIs and protease inhibitors (PIs) in phase IIb studies.^{4,5}
- We reviewed the efficacy and safety of TMC125 in treatment-experienced and treatment-naïve patients, and also describe drug-drug interaction data

Methods

- Proof of principle, efficacy and safety study designs are described in **Table 1**

Table 1. Study designs

	TMC125-C208 ⁶	TMC125-C207 ⁷	TMC125-C203	TMC125-C223 ⁸
	N=19	N=16	N=240	N=199
Primary objective	Proof of principle	Proof of principle	Safety and tolerability	Dose finding
Patient segment	ARV-naïve	NNRTI-resistant	Three-class experienced	NNRTI- and PI-resistant
TMC125 dose, mg bid	900 (PEG 4,000 formulation)	900 (PEG 400 formulation)	400, 800, or 1,200 (TF035 formulation), each with OBR*	400 or 800 (TF035 formulation), each with BR*
Control	Placebo	None	Placebo + OBR	Standard of care
Treatment duration	7 days	7 days	48 weeks ⁴	48 weeks

OBR = optimized background regimen; BR = background regimen; ARV = antiretroviral
*3-4 ARVs (1-4 NRTIs ± 1 LPV/r or SQV/r ± ENF); *Investigator selected NRTIs ± LPV/r ± ENF; *Study completers who would benefit from TMC125 were eligible to enter roll-over trial TMC125-C211 or TMC-C229

Results

- Two proof-of-principle studies were conducted with TMC125 (**Figure 1**)
 - In treatment-naïve patients, the mean reduction in HIV-1 RNA was 1.99 copies/mL after 7 days of TMC125 monotherapy⁶
 - In patients with NNRTI resistance, the mean reduction in HIV-1 RNA was 0.9 copies/mL after 7 days of TMC125 functional monotherapy⁷

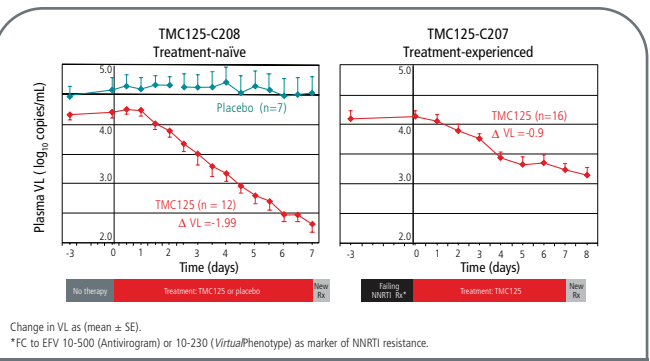


Figure 1. TMC125-C208 and TMC125-C207: Viral load decrease in proof-of-principle trials

- The safety and tolerability of TMC125 in treatment-experienced patients was assessed in **TMC125-C203**, a phase IIb, placebo-controlled study (**Figure 2**)

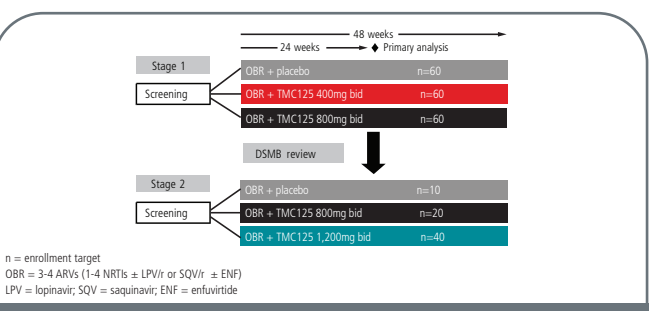


Figure 2. TMC125-C203: Study design.

- No substantial differences were seen in the rates of the most common AEs (diarrhea, headache, rash, and nausea) between TMC125 and placebo (**Table 2**)⁹

Table 2. TMC125-C203: Most common AEs

AE, (%)	TMC125				Placebo + OBR (n=66)	95% CI All TMC125 versus placebo
	400mg bid (n=57)	800mg bid (n=74)	1,200mg bid (n=43)	All TMC125 (N=174)		
Median treatment duration (weeks)	47	32	24	29	40	-
Any AE	88	95	93	92	91	-7.0 to 9.1
Diarrhea	30	24	26	26	38	-24.9 to 2.0
Headache	28	18	9	19	17	-8.4 to 13.0
Rash	16	18	19	17	11	-2.7 to 15.9
Nausea	18	18	14	17	23	-17.6 to 5.0
URT ¹	9	15	12	12	14	-11.2 to 8.0
Abdominal pain	11	12	12	12	8	-4.0 to 11.9
Fatigue	12	5	19	11	9	-6.6 to 10.0

URT¹ = upper respiratory tract infection.

- Grade 3/4 adverse events (AEs) were not substantially different from placebo
- There was no clear dose-response relationship with safety assessments
- Rashes were generally mild to moderate:
 - Overall incidence of rash was 17% across all doses of TMC125 and 11% for placebo (95% CI: for the difference: -2.7 to 15.9), with no differentiation by dose
 - Eight percent of rashes (one case of Grade 3) were reported at least possibly related to TMC125
 - No Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiform were reported in this study
 - Rash led to permanent discontinuation in 3 (2%) TMC125 patients and 1 (2%) placebo patients
 - No association was observed with baseline CD4 cell count or gender
- In general, neuropsychiatric AEs in TMC125-treated patients were mild to moderate in severity, and not reported more frequently than with placebo¹⁰ (**Table 3**)

Table 3. TMC125-C203: Neuropsychiatric disorders

	TMC125 n (%)	Placebo n (%)
Nervous disorders		
Dizziness	18 (10)	3 (5)
Headache	33 (19)	11 (17)
Insomnia	10 (6)	3 (5)
Psychiatric disorders		
Anxiety	3 (2)	1 (2)
Depression	7 (4)	4 (6)
Sleep Disorder	3 (2)	1 (2)

- TMC125-C227** was an exploratory trial to investigate the efficacy and tolerability of TMC125 following first-line NNRTI failure⁹
 - A phase II randomized, active-controlled, open-label exploratory trial in PI-naïve patients with documented evidence of NNRTI resistance
 - Study arms: TMC125 800mg bid + 2 NRTIs vs active control (1 PI + 2 NRTIs)
 - The trial was discontinued when it was found that a lower proportion of patients achieved and maintained a viral load (VL) <50 copies/mL after 12 weeks of therapy in the TMC125 group compared to the control group
 - Subsequent analysis revealed that the level of both NRTI and NNRTI resistance was higher than what might have been expected from a first-line failure population
 - Greater than one-third of patients recycled at least one NRTI, and ≥20% of patients had ≥4 NRTI mutations
 - A high number of NNRTI mutations were present in this population (=40% of patients had 2 NNRTI mutations, 23% had 3 NNRTI mutations, and 5% had 4 NNRTI mutations)
 - Increasing numbers of thymidine analogue mutations and M184V were associated with increased NNRTI resistance at baseline
 - The combination of high-level NRTI and NNRTI resistance adversely impacted the TMC125 arm
 - Consistent with treatment guidelines, patients failing a first-generation NNRTI should immediately switch their regimen to avoid the accumulation of multi-class resistance
- In **TMC125-C223**, a phase IIb, dose-finding study, patients with documented NNRTI resistance and at least 3 primary PI mutations were randomized 1:2:2 to an active control or one of 2 doses of TMC125 (**Figure 3**)
 - The primary endpoint was mean change in VL from baseline at Week 24
 - Patient baseline characteristics are described in **Table 4**
 - The median number of primary PI, NNRTI, and NRTI mutations at screening was 4, 2, and 6, respectively

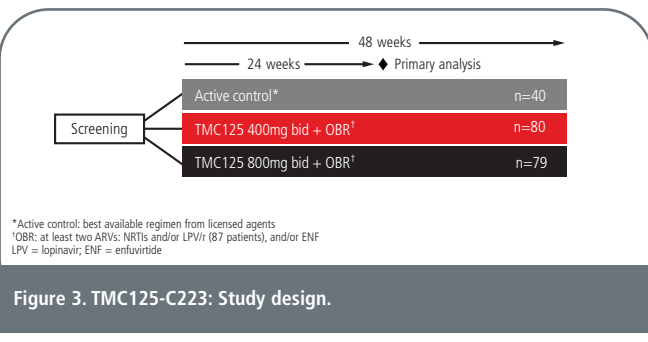


Figure 3. TMC125-C223: Study design.

Table 4. TMC125-C223: Baseline patient characteristics, treatment history, and resistance profile at baseline⁸

Parameter	TMC125		Control n = 40	All patients N = 199
	400mg bid n = 80	800mg bid n = 79		
Sex, n (%)				
Male	74 (92.5)	71 (89.9)	37 (92.5)	182 (91.2)
Median age, years (range)	46 (33–63)	46 (29–63)	44 (18–64)	46 (18–64)
Ethnic origin, n (%)				
White	45 (56.3)	47 (59.5)	29 (72.5)	121 (60.8)
Black	17 (21.3)	15 (19.0)	7 (17.5)	39 (19.6)
Hispanic	16 (20.0)	17 (21.5)	3 (7.5)	36 (18.1)
Other or not known	2 (2.5)	0 (0.0)	1 (2.5)	3 (1.5)
Median baseline VL, log ₁₀ copies/mL (range)	4.67 (2.61–5.85)	4.69 (3.10–6.54)	4.69 (3.32–7.05)	4.68 (2.61–7.05)
Median baseline CD4 cell count, cells/mm ³ (range)	91.0 (1.0–433.0)	102.0 (1.0–564.0)	100.0 (1.0–658.0)	98.5 (1.0–658.0)
Median duration of HIV infection, years (range)	14.5 (6.0–21.6)	14.8 (3.5–22.7)	14.6 (2.2–22.6)	14.6 (2.2–22.7)
Median fold change in EC ₅₀ (range) [§]	n = 80	n = 78	n = 39	n = 197
Efavirenz	49.8 (0.4–17,889.1)	46.2 (0.3–17,421.6)	24.6 (0.6–7,732.8)	41.4 (0.3–17,889.1)
TMC125	1.6 (0.1–295.6)	2.0 (0.1–398.8)	1.4 (0.4–123.6)	1.7 (0.1–398.8)

EC₅₀ = 50% effective concentration.
[§]From October 2004 IAS-USA list supplemented with additional known NNRTI resistance-associated mutations.
[¶]90, 81, and 95% of subjects from the TMC125 400mg, 800mg and control groups, respectively, had NNRTI mutations at screening. The remainder had historical genotypic NNRTI resistance.
[§]Assessed by Antivirogram and expressed as fold-change EC₅₀ against patient isolate relative to wild-type HIV-1.

- The mean change from baseline in VL at Week 24 and Week 48 was significantly greater for both TMC125 arms versus placebo, as shown in **Figure 4**⁴
 - No statistical difference in virologic response was observed between the TMC125 groups

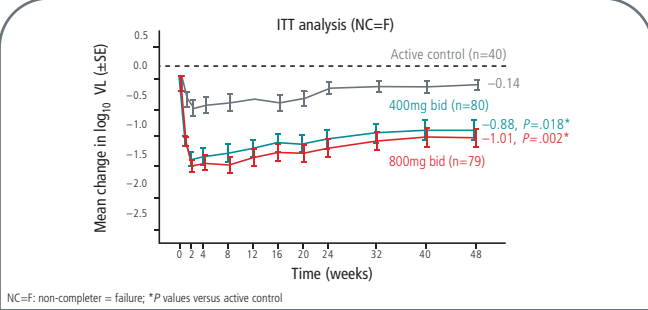


Figure 4. TMC125-C223: Change in VL from baseline to Week 48.

- Analysis of response by baseline resistance showed that activity was retained in the presence of multiple NNRTI mutations where currently approved NNRTIs are not expected to be active⁴ (**Figure 5**)
 - Even in patients with ≥3 NNRTI mutations, the mean reduction in VL was greater than the control group

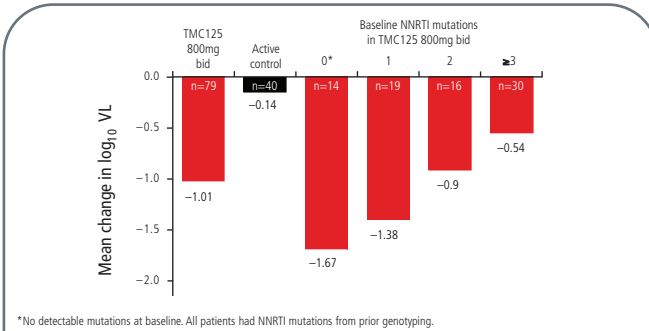


Figure 5. TMC125-C223: Number of detectable NNRTI mutations at baseline vs. virologic response at Week 48.

- In vitro* analysis of mutations associated with NNRTI resistance
 - Given the development of next-generation NNRTIs with a higher barrier to resistance and early evidence of their activity in the presence of NNRTI mutations, a comprehensive list of 41 mutations associated with NNRTI resistance was developed to guide *in vitro* and clinical research with NNRTIs¹¹
 - To determine the frequency of these mutations in the Virco database, 19,689 HIV-1 recombinant isolates with at least one NRTI or one primary PI mutation and collected between 2004 and 2006 were assessed.
 - K103N and Y181C were the most prevalent mutations
- The prevalence of individual NNRTI resistance-associated mutations (RAMs) is illustrated in **Figure 6**

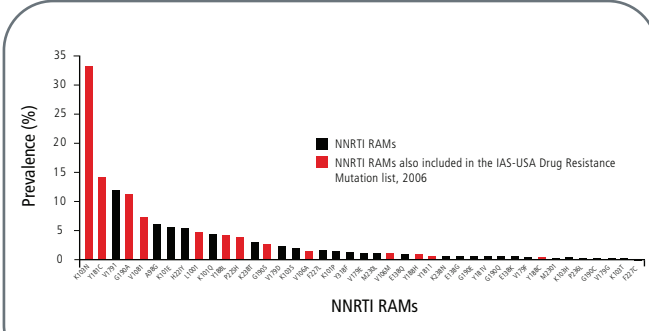


Figure 6. Prevalence of NNRTI RAMs among 19,689 HIV-1 recombinant clinical isolates.¹¹

- Twenty-four clinical drug-drug interaction studies with medications commonly used in HIV treatment with TMC125 have been conducted to date¹² (**Table 5**)
 - Within current clinical studies, TMC125 may be co-administered without dose adjustment with boosted PIs (except tipranavir/ritonavir or fosamprenavir/ritonavir) with NRTIs and with omeprazole, famotidine, oral contraceptives, or methadone
 - Co-administration with clarithromycin is not recommended for the treatment of *Mycobacterium avium* complex
 - PK interactions with commonly coadministered medications are predictable and manageable

Table 5. Summary of drug-drug interaction studies: Dose adjustment recommendations in current clinical trials.

No dose adjustment of TMC125 or co-administered drug required	Modify dose or schedule of co-administered drug	Co-administration not recommended
<ul style="list-style-type: none"> Atazanavir Darunavir Lopinavir Tenofovir Didanosine Omeprazole Ranitidine Rifabutin Methadone Oral contraceptives (ethinylestradiol/norethindrone) 	<ul style="list-style-type: none"> Fosamprenavir* Sildenafil† Clarithromycin‡ 	<ul style="list-style-type: none"> Unboosted PIs <ul style="list-style-type: none"> Atazanavir Indinavir Saquinavir Tipranavir Full-dose ritonavir Nevirapine Efavirenz

*Fosamprenavir: dose adjustment of fosamprenavir might be considered when combined with TMC125; no dose adjustment is necessary for TMC125
†Sildenafil: concomitant administration of TMC125 and sildenafil is allowed; dose adjustment of sildenafil may be tailored to the clinical response.
‡Clarithromycin: dose adjustment for clarithromycin should be considered in patients with impaired renal function; co-administration with clarithromycin is not recommended for the treatment of *Mycobacterium avium* complex

- The DUET phase III clinical trials to assess the efficacy, safety, and tolerability TMC125 in treatment-experienced patients are underway
 - Randomized, double-blind, placebo-controlled trials with identical design
 - TMC125 is dosed at 200mg bid, utilizing a new formulation that provides comparable exposure to the phase II 800mg bid dose
 - The background regimen for both arms includes darunavir/r plus investigator-selected NRTIs ± ENF
 - Primary endpoint: proportion of patients with VL <50 copies/mL at 24 weeks

Conclusions

- TMC125 is a next-generation NNRTI with potent *in vitro* activity against wild-type and NNRTI-resistant HIV-1
- In the TMC125-C223 phase IIb study, VL reduction was maintained through 48 weeks in NNRTI-resistant treatment-experienced patients
 - TMC125 retained activity in the presence of multiple NNRTI mutations where current NNRTIs are not expected to be effective
- TMC125 is generally safe and well tolerated and in TMC125-C203 was not associated with an increase in neuropsychiatric AEs compared with placebo
- PK interactions of TMC125 with medications commonly used in HIV therapy are well characterized and manageable
- Phase III trials are ongoing to assess the efficacy, safety, and tolerability of a new formulation of TMC125 200mg bid in treatment-experienced patients

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