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Efficacy and safety results at 48 weeks with the novel NNRTI, TMC125, and impact of baseline resistance on the virologic response in study TMC125-C223

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Abstract

Methods
TMC125-C223 is a randomized, controlled study of TMC125 in 199 patients with documented NNRTI resistance and ≥3 primary protease inhibitor (PI) mutations. Patients were randomized to TMC125 (400mg or 800mg bid) with an investigator selected background, or standard-of-care control regimen.

Results
Median baseline viral load (VL) was 4.7 $\log_{10}$ copies/mL and CD4 count 100 cells/mm^3. At 48 weeks, the mean reduction in $\log_{10}$ VL (intent-to-treat (ITT), non-completer = failure) was –0.88, –1.01 and –0.14 for the 400mg, 800mg and control arms, respectively, the difference for both TMC125 doses versus control was statistically significant ($p<0.05$). CD4 cell counts increased by 58, 61 and 13 for the 400mg, 800mg and control arms, respectively.

Virologic failure on both TMC125 arms was 9%; in the control arm, 98% of patients discontinued study, 78% due to virologic failure. The comparison of safety was confounded by the lower median duration of treatment in the control arm of 17.9 weeks, versus 47.7 weeks in both TMC125 groups. Grade 3 and 4 adverse events (AEs) (all causes) were reported in 43% of patients on TMC125; 17% discontinued due to AEs. At baseline, patients had a median of two NNRTI mutations and the phenotypic median fold-change (FC) to efavirenz, nevirapine and TMC125 was 41, 61, and 1.7, respectively.

The virologic response by number of NNRTI mutations at baseline is shown for the 800mg group (dose selected for Phase III development as new 200mg formulation).

No. of mutations	0	1	2	≥3
N (%)	14 (18%)	19 (24%)	16 (20%)	30 (38%)
Mean Δ VL	–1.67	–1.38	–0.90	–0.54

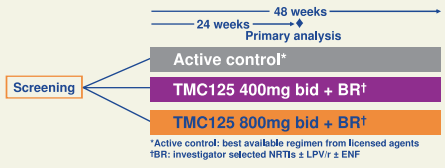
Conclusions
In this study, TMC125 showed high rates of sustained efficacy at 48 weeks in heavily pretreated patients. The analysis of response by baseline resistance shows that TMC125 retains activity in the presence of multiple NNRTI mutations where current NNRTIs are not expected to be effective.

Introduction

- TMC125 is an NNRTI designed to have a high genetic barrier to the development of resistance[1,2]
  - TMC125 was selected as it maintains activity despite common NNRTI mutations
- Data from TMC125-C207, a 7-day Phase IIa Proof of Principle trial with functional monotherapy in NNRTI-resistant patients, showed a mean change in $\log_{10}$ VL of –0.9[3]
- Data from the 48-week efficacy analysis of the Phase IIb trial TMC125-C223 in heavily pretreated patients with substantial NNRTI and PI resistance were presented recently[4,5]

1. Andries K, et al. Antimicrob Agents Chemother 2004;48:4680–6
2. Vingerhoets J, et al. J Virol 2005;79:12773–82
3. Gazzard BG, et al. AIDS 2003;17:F49–F54
4. Nadler J, et al. 10th EACS 2005 (Abstract LBPS3/7A)
5. Cohen C, et al. 12th BHIVA 2006 (Poster 2)

TMC125-C223: study design



*Active control: best available regimen from licensed agents
†BR: investigator selected NRTIs ± LPV/r ± ENF

- Documented NNRTI resistance and ≥3 primary PI mutations
- Partially blinded, US, randomization 1:2:2 (active control versus 400mg bid versus 800mg bid)
- VL >1,000 copies/mL
- The study protocol was reviewed and approved by the appropriate institutional ethics committee(s) and health authorities, and was conducted in accordance with the Declaration of Helsinki

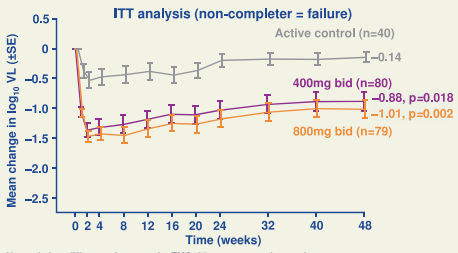
BR = background regimen; LPV = lopinavir; ENF = enfuvirtide

TMC125-C223: treatment-experienced population

	Median (range)
VL ($\log_{10}$ copies/mL)	4.7 (2.6–7.1)
CD4 count (cells/mm^3)	99 (1–660)
Duration of HIV infection (years)	14.6 (2.2–22.7)
Number of mutations	
NNRTI resistance-associated mutations	2 (0–5)
NRTI resistance-associated mutations	6 (0–12)
Primary PI mutations	4 (0–6)
PI resistance-associated mutations	9 (0–13)
Resistant to all currently approved PIs (excluding tipranavir)*	83%†
Phenotypic susceptibility score (PSS)	1 (0–4)‡
FC to TMC125	1.7 (0.1–399)
FC to lopinavir	83.6 (not different between groups)

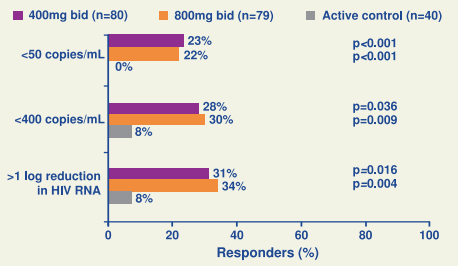
*Tipranavir was not approved when study TMC125-C223 was started; †FC to LPV was 83.6 (82.7–84.3 across study arms); ‡ENF is included in this PSS and scored as sensitive if not previously used; TMC125 is excluded from the PSS; PSS was 1 for all study arms

TMC125-C223 primary endpoint: change in VL at 48 weeks



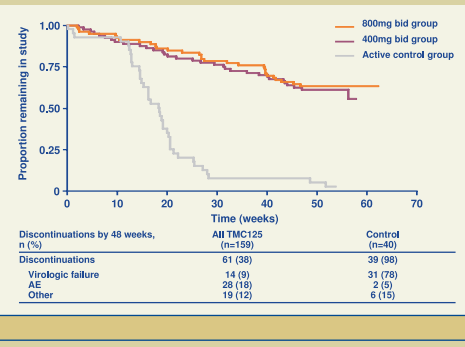
No statistical difference between the TMC125 groups was observed
Ethylenediaminetetraacetic acid samples and Roche Amplicor® version 1.5 used for HIV RNA analyses
p values versus active control; SE = standard error

TMC125-C223: virologic response* at Week 48



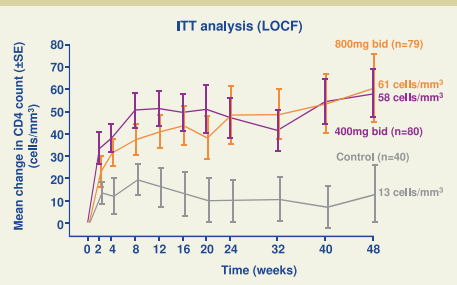
p values versus active control
*Time to loss of virologic response (TLOVR), based on FDA definition

TMC125-C223: time to discontinuation



Discontinuations by 48 weeks, n (%)	All TMC125 (n=159)	Control (n=40)
Discontinuations	61 (38)	39 (98)
Virologic failure	14 (9)	31 (78)
AE	28 (18)	2 (5)
Other	19 (12)	6 (15)

TMC125-C223: change in CD4 count



LOCF = last observation carried forward

TMC125-C223: safety – overview

- Safety comparisons confounded due to high rate of treatment discontinuations in control group, leading to substantial difference in treatment durations between groups
- AEs reported in 99% in TMC125 groups and 78% in control
- Both TMC125 doses were equally well tolerated

Most common AEs, n (%)	All TMC125 (n=159)	Active control (n=40)
Median treatment duration	48 weeks	18 weeks
Diarrhea	35 (22)	6 (15)
Any rash	32 (20)	3 (8)
Injection-site reaction	32 (20)	10 (25)
Pyrexia	32 (20)	4 (10)
Fatigue	25 (16)	6 (15)
Headache	25 (16)	2 (5)
Nausea	24 (15)	6 (15)
Lymphadenopathy	22 (14)	4 (10)
Insomnia	21 (13)	4 (10)

TMC125-C223: clinical safety

AEs, n (%)	All TMC125 (n=159)	Active control (n=40)
Median treatment duration	48 weeks	18 weeks
Any grade 3	62 (39)	9 (23)
Any grade 4	21 (13)	5 (13)

- Specific grade 3/4 AEs in ≥3 patients in TMC125 groups
  - pneumonia: four patients
  - abdominal pain: three patients
  - drug-related rash: three patients; no grade 4 rash was seen
  - hypertriglyceridemia: three patients
  - pancreatitis: three patients (all had elevated amylase and lipase; all recovered and had known risk factors)
- Four deaths: three (2%) in 400mg bid group and one (3%) in control
  - one death (cardiopulmonary failure and myocardial infarction [MI]) in 400mg bid group considered possibly related to TMC125

TMC125-C223: laboratory abnormalities

Laboratory parameters, n (%)	All TMC125 (n=159)	Active control (n=40)
Median treatment duration	48 weeks	18 weeks
Any grade 3/4 abnormality	62 (39)	14 (35)
Any grade 3 abnormality	57 (36)	13 (33)
Any grade 4 abnormality	17 (11)	6 (15)

- No dose difference for any laboratory abnormality
- Most common grade 3/4 laboratory abnormalities for TMC125 and active control were
  - triglycerides: 14 (9%) and 4 (11%) patients
  - pancreatic amylase: 13 (8%) and zero patients
  - neutropenia: 12 (8%) and 4 (11%) patients
  - creatinine: 6 (4%) and zero patients

TMC125-C223: safety – serious adverse events (SAEs)

- SAEs were reported in 27% in the TMC125 groups with no dose differentiation
- SAEs at least possibly related to TMC125
  - three in 400mg group (cardiopulmonary failure, MI, hemorrhagic stroke)
  - one in 800mg group (pancytopenia)
- No trend for type of possibly related SAEs

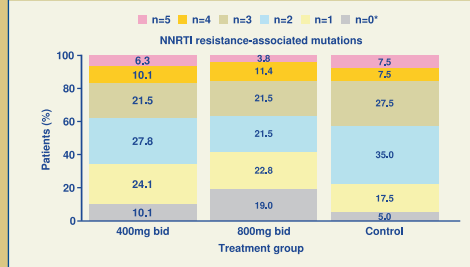
System organ class, preferred term n (%)	TMC125 400mg bid (n=80)	TMC125 800mg bid (n=79)	All TMC125 (n=159)	Control (n=40)
Any SAE	21 (26)	22 (28)	43 (27)	7 (18)
Blood and lymphatic system disorders				
Pancytopenia	1 (1)	1 (1)*	2 (1)	0
Cardiac disorders				
Cardiopulmonary failure	1 (1)*	0	1 (1)	0
MI	2 (3)†	0	2 (1)	0
Nervous system disorders				
Hemorrhagic stroke	1 (1)*	0	1 (1)	0

*Possibly related to TMC125; †one case possibly related; one case not related

Objectives of the current analysis

- Investigate baseline resistance parameters
  - genotype – phenotype
  - mutations associated with increased baseline
  - FC in EC_{50} values to TMC125
  - ITT analysis, all patients included
- Investigate virologic response associated with the number of baseline NNRTI mutations
  - imputed (NC=F) data
  - only the TMC125 800mg bid was included *(comparable to the 200mg bid dose of the new formulation used in the Phase III studies)*

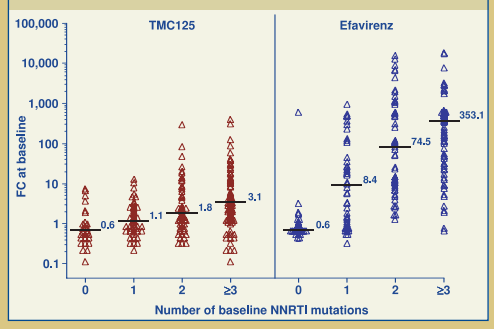
TMC125-C223: baseline resistance – genotype



- Most frequent mutations: K103N, Y181C and G190A

*All patients had at least one NNRTI mutation at screening or from prior genotyping

TMC125-C223: baseline resistance – phenotype

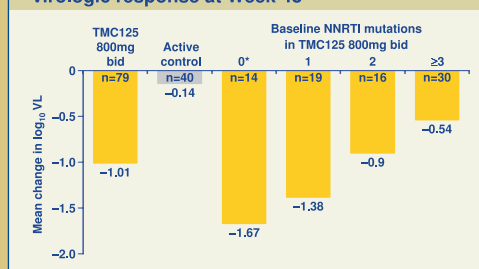


Baseline NNRTI mutations associated with a TMC125 FC >10 (arbitrary threshold)

- The geometric mean FC to TMC125 for each NNRTI mutation present at baseline was determined
- There was no single NNRTI mutation that was associated with a mean FC >10 (arbitrary threshold) to TMC125
  - clinically relevant FC to be determined from larger data sets
- Frequency of combinations of NNRTI mutations associated with a mean TMC125 FC >10 was low (12%)
- Each of the following mutations, always in combination with up to four other mutations, were associated with a mean FC >10
  - K101P, V179E, V179F, Y181I, Y181V, G190S, M230L
  - for V179E, V179F, G190S or M230L: the additional mutations always included Y181C when the FC >10
- These mutations were previously identified *in vitro* to be associated with an increased FC to TMC125

1. Vingerhoets J, et al. J Virol 2005;79:12773–82

TMC125-C223: number of NNRTI mutations and virologic response at Week 48



- Patients discontinuing the trial for any reason had their VL response imputed as no change from baseline (NC=F)

*All patients had NNRTI mutations from prior genotyping

Conclusions

Efficacy and safety

- In this study, TMC125 showed high rates of sustained efficacy at 48 weeks in heavily pretreated patients.
- There were no dose-related effects on safety and tolerability.
- TMC125 retains activity in the presence of multiple NNRTI mutations where current NNRTIs are not expected to be effective.

Baseline resistance and VL response

- Baseline FC to TMC125 in this highly treatment-experienced population was low and increased with higher number of NNRTI mutations.
- There was no single NNRTI mutation that was associated with a FC >10 (arbitrary threshold) to TMC125.
- The mean change in VL in the TMC125 800mg bid group (imputed data) was
  - 0.90 $\log_{10}$ or greater in patients with ≤2 NNRTI mutations
  - 0.54 $\log_{10}$ in patients with three or more NNRTI mutations.

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