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Pooled 24-week results of DUET-1 and DUET-2: efficacy of TMC125 (etravirine; ETR) in treatment-experienced HIV-1-infected patients

P7.3/11

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Abstract

Objectives: TMC125 is a next-generation NNRTI with potent activity against HIV-1, including viruses with NNRTI resistance-associated mutations (RAMs). DUET-1 and DUET-2 are ongoing, randomised, placebo-controlled, double-blind, Phase III trials designed to show superiority of TMC125 plus background regimen (BR) over placebo plus BR in treatment-experienced HIV-1-infected patients. Trials differed only by geographical location. We report efficacy findings from planned, pooled analyses when patients reached Week 24 (or discontinued).

Methods: Patients with documented ≥1 NNRTI-RAMs at study entry and ≥3 primary protease inhibitor (PI) mutations were randomised to TMC125 200mg or placebo twice-daily with BR of darunavir/ritonavir (DRV/r), optimised NRTIs and optional enfuvirtide (ENF). The primary endpoint was proportion of patients with confirmed viral load <50 copies/mL at Week 24 (intent-to-treat population [ITT] time to loss of virological response imputation algorithm [TLOVR]). Primary analysis was according to ENF use (*de novo* versus re-using or not using).

Results: Baseline characteristics were generally similar across treatment arms. Overall, TMC125 was superior to placebo for efficacy endpoints (viral load <50 copies/mL: 59% vs 41%). TMC125 demonstrated a high barrier to resistance, with ≥3 TMC125-RAMs (selected NNRTI-RAMs) required to substantially reduce virological responses.

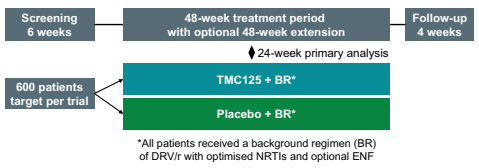
Table. Baseline characteristics and efficacy endpoints in the overall population

	TMC125 + BR (n=599)	Placebo + BR (n=604)
Baseline characteristics		
HIV RNA, $\log_{10}$ copies/mL (median)	4.8	4.8
CD4 cell count, cells/mm³ (median)	99	109
Virology endpoints at Week 24*		
Viral load <50 copies/mL (%)‡	59§	41
Viral load <400 copies/mL (%)	74§	53
Viral load reduction from baseline, $\log_{10}$ copies/mL	2.4§	1.7
Immunological endpoints at Week 24		
CD4 cell count change from baseline, cells/mm³	86§	67

*Predictors of improved virological response were lower baseline viral load, greater number of active background antiretrovirals (ARVs), ENF use, lower TMC125 fold change (FC), fewer RAMs and lower DRV FC (p<0.0001). ‡In patients receiving de-novo ENF, and accounting for DRV FC, significantly more patients responded with TMC125 than placebo (73% vs 62%; p<0.05). §p value vs placebo; p<0.0001

Conclusions: At 24 weeks, in patients with NNRTI-resistant virus, TMC125 plus BR provided superior virological and immunological response versus placebo plus BR.

DUET study design and major inclusion criteria



- DUET-1 and DUET-2 differed only in geographical location; pooled analysis was pre-specified
- Major inclusion criteria
  - plasma viral load >5,000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
  - ≥1 NNRTI mutation,‡ at screening or in documented historical genotype
  - ≥3 primary PI mutations at screening
- Patients recruited from Thailand, Australia, Europe and the Americas

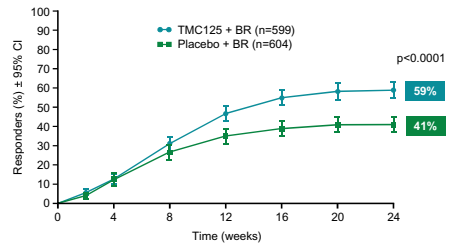
‡From extended list of NNRTI mutations[1]

Baseline characteristics and background ARVs

Parameter, % or median (range)		TMC125 + BR (n=599)	Placebo + BR (n=604)
Patient demographics	Male (%)	90	89
	Caucasian (%)	70	70
Disease characteristics	Viral load ($\log_{10}$ copies/mL)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
	CD4 cells (cells/mL)	99 (1.0–789)	109 (0.0–912)
	CDC category C (%)	58	59
Prior ARV use	10–15 ARVs (%)	66	64
	DRV/r (%)	4	5
Detectable mutations	≥2 NNRTI RAMs* (%)	66	66
	≥4 primary PI RAMs (%)	62	63
BR	Used ENF (total; %)	46	47
	Used ENF *de novo* (%)	26	27
	Active background agents‡ = 0 (%)	17	16
	Active background agents‡ = 1 (%)	36	39

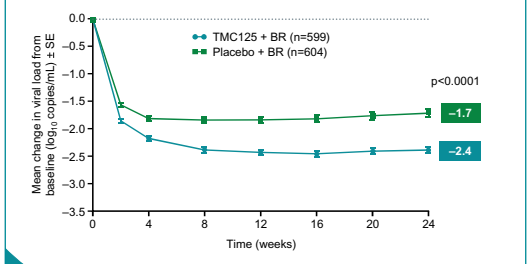
*From extended list of NNRTI mutations[1]; ‡assessed by phenotypic sensitivity score (PSS)

Patients with viral load <50 copies/mL at Week 24 (primary endpoint; ITT TLOVR)



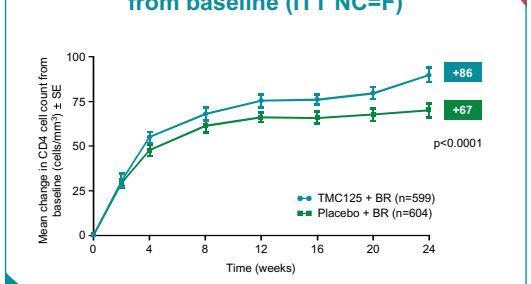
CI = confidence interval

Viral load reduction from baseline (ITT NC=F)

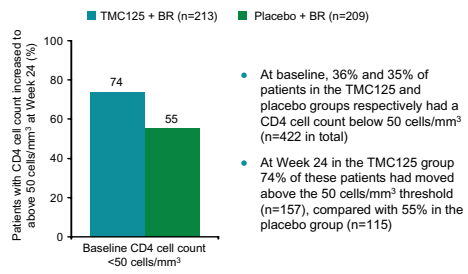


SE = Standard error; NC=F = non-completer equals failure imputation algorithm; changes below the detection limit (<50 copies/mL) were imputed as 49 copies/mL

Change in CD4 cell count from baseline (ITT NC=F)



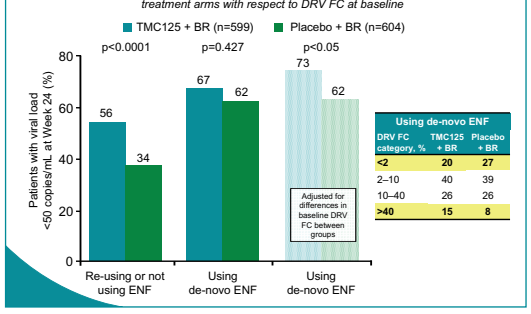
CD4 cell count increase to 50 cells/mm³ or above



- At baseline, 36% and 35% of patients in the TMC125 and placebo groups respectively had a CD4 cell count below 50 cells/mm³ (n=422 in total)
- At Week 24 in the TMC125 group 74% of these patients had moved above the 50 cells/mm³ threshold (n=157), compared with 55% in the placebo group (n=115)

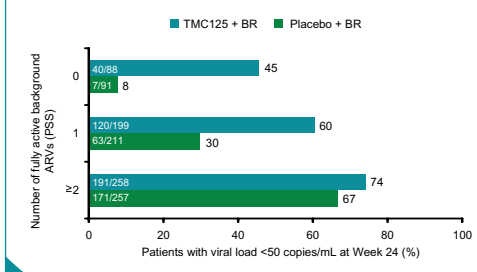
Response (<50 copies/mL) according to ENF use (primary analysis)

NB: in patients using ENF de novo, there was an imbalance between treatment arms with respect to DRV FC at baseline



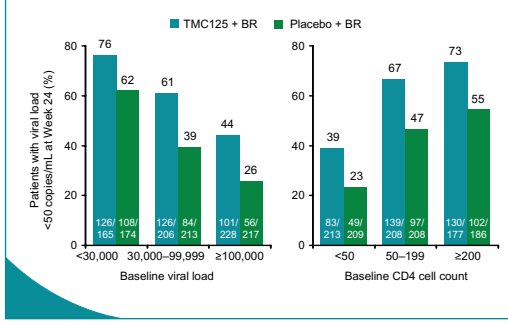
Using de-novo ENF		
DRV FC category, %	TMC125 + BR	Placebo + BR
<2	20	27
2–10	40	39
10–40	26	26
>40	15	8

Response (<50 copies/mL) according to number of active background ARVs

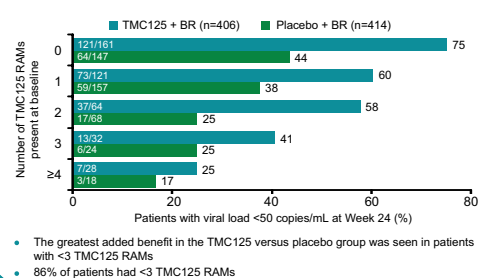


Analysis excludes patients who discontinued except for virological failure; DRV and ENF are counted as fully active if FC <10 or used *de novo*, respectively

Response (<50 copies/mL) according to baseline viral load and CD4 cell count



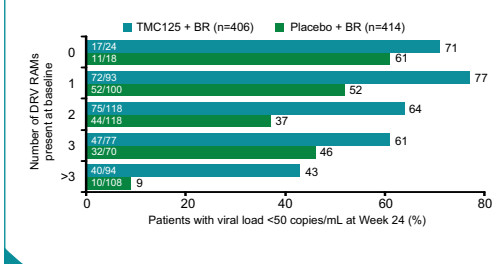
Response (<50 copies/mL) according to number of TMC125 RAMs



- The greatest added benefit in the TMC125 versus placebo group was seen in patients with <3 TMC125 RAMs
- 86% of patients had <3 TMC125 RAMs

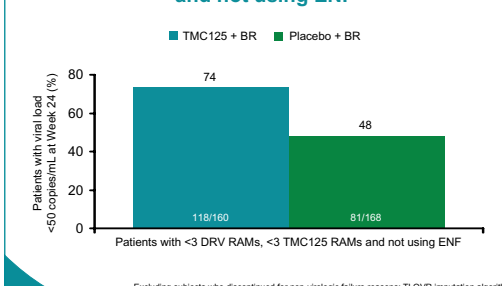
13 baseline RAMs were associated with a decreased response to TMC125 (TMC125 RAMs)[3]: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S. These RAMs occurred mainly in the presence of other NNRTI RAMs; analysis excludes patients who used de-novo ENF or discontinued except for virological failure

Response (<50 copies/mL) according to number of DRV RAMs



11 baseline RAMs are associated with a decreased response to DRV (DRV RAMs)[2]: V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V and L89V; analysis excludes patients who used de-novo ENF or discontinued except for virological failure

Virological response (<50 copies/mL) when using active DRV*, active TMC125‡ and not using ENF



Excluding subjects who discontinued for non-virologic failure reasons; TLOVR imputation algorithm; *defined as <3 DRV RAMs; ‡defined as <3 TMC125 RAMs

Conclusions

- In treatment-experienced patients, including those with NNRTI resistant virus, TMC125 consistently demonstrated superiority over placebo
  - 59% of patients achieved confirmed undetectable viral load <50 copies/mL (undetectable) with TMC125 plus BR at Week 24.
- Even in the absence of any other fully active background agents, with TMC125, 45% of patients achieved <50 copies/mL viral load
  - response rates increased as more active agents were used in the BR.
- Higher responses were apparent with TMC125 irrespective of baseline viral load or CD4 cell count.
- Thirteen TMC125 RAMs were identified
  - the greatest added benefit in the TMC125 versus placebo group was seen in patients with <3 TMC125 RAMs
  - 86% of patients had <3 TMC125 RAMs.
- TMC125 demonstrated significant activity and provides a new treatment option for patients with resistance to other NNRTIs.

References

1. Tambuyzer L, et al. EHDRW 2007. Abstract 67.
2. de Béthune MP, et al. EHDRW 2006. Abstract 51.
3. Vingerhoets J, et al. IHDRW 2007. Abstract 32.

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DUET-1
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