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

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Abstract

Objectives: DUET-1 and DUET-2 are identically designed, ongoing, randomised, double-blind, placebo-controlled, Phase III trials, investigating TMC125 versus placebo in HIV-1-infected, treatment-experienced patients. The trials differ only by geographical location. We report findings from a planned, pooled analysis of safety in DUET-1 and DUET-2 when all patients had reached Week 24 or discontinued.

Methods: Patients on stable virologically-failing treatment, with documented NNRTI resistance (historical and/or at study entry) and ≥3 primary protease inhibitor (PI) mutations were randomised 1:1 to TMC125 200mg or placebo twice daily (each with darunavir/ritonavir [DRV/r], optimised NRTIs and optional enfuvirtide [ENF]). Prespecified intent-to-treat (ITT) analyses of rash, nervous system, psychiatric and hepatic adverse events (AEs) were by Fisher's exact test.

Results: 1,203 patients were treated (89.3% male; 69.8% Caucasian; 58.4% CDC category C), with median baseline viral load of 4.8 $\log_{10}$ copies/mL and CD4 cell count of 105 cells/mm^3. Patients (n=599) received TMC125 for a median treatment duration of 30 weeks. The safety and tolerability findings are summarised in the table.

Incidence, %	TMC125 (N=599)	Placebo (N=604)
All AEs	92.5	92.5
Any grade 3/4 AEs	24.7	27.2
Discontinued due to AE	5.8	4.5
Any serious AE	13.2	18.7
Serious AE attributed to study drug	2.3	2.5
Deaths (any cause)	1.3	2.5
Most common AEs		
Rash (any type)*	17.0	9.4
Discontinued due to rash	2.2	0.0
Diarrhoea	15.0	20.4
Nausea	13.9	11.1
AEs of specific interest (grouped terms)		
Nervous system‡	14.9	18.5
Psychiatric§	12.9	15.1
Hepatic¶	5.3	5.1
Selected grade 3/4 laboratory abnormalities**		
Triglycerides	7.0	4.3
Total cholesterol	5.8	4.1
LDL cholesterol	5.2	5.4
AST	2.5	1.7
ALT	2.5	1.7
Pancreatic amylase	7.5	7.9

*p=0.0001. Rashes occurred more frequently with TMC125 than placebo, but were generally grade 1/2 in severity (1.3% of patients experienced grade 3 rash). Rashes were more common in women (28.3% vs 15.8% men) and not related to CD4 cell count. Events generally started 1–2 weeks following treatment-initiation and resolved on continued treatment. ‡p=0.0896; §p=0.2803; ¶p=0.8976; **No consistent or clinically relevant changes in laboratory or ECG parameters were reported.

Conclusions: The incidence and severity of AEs with TMC125, including neuropsychiatric AEs, were generally similar to placebo. Rash, generally mild-to-moderate and self-limited, was the only AE to occur more frequently with TMC125 than placebo.

Please note that these data have been updated following submission of this abstract.

Grade 3 and 4 AEs

AE regardless of causality, n (%)	TMC125 group (n=599)	Placebo group (n=604)
Any grade 3 or 4 AE	148 (24.7)	164 (27.2)
Most common grade 3 and 4 AEs (>0.5% in pooled TMC125 group)*		
Hypertriglyceridaemia	11 (1.8)	4 (0.7)
Neutropaenia	9 (1.5)	18 (3.0)
Rash (any type)	8 (1.3)	0
Anaemia	7 (1.2)	6 (1.0)
Peripheral neuropathy	6 (1.0)	0
Thrombocytopaenia	5 (0.8)	3 (0.5)
Hypercholesterolaemia	4 (0.7)	4 (0.7)
Pancreatitis	4 (0.7)	0
Pneumocystis jiroveci pneumonia	4 (0.7)	4 (0.7)
Renal failure	4 (0.7)	2 (0.3)

*Including grade 3 and 4 laboratory abnormalities reported as AEs and excluding injection site reactions

Treatment-emergent laboratory abnormalities*

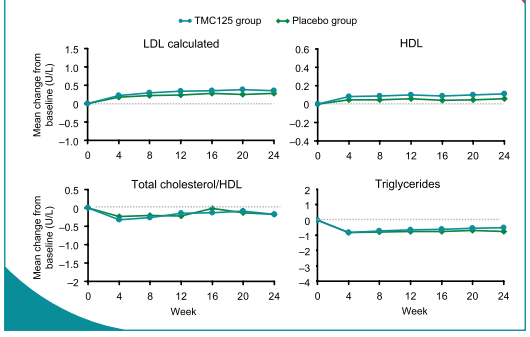
Parameter, n (%)	TMC125 group (n=599)	Placebo group (n=604)
At least one laboratory abnormality	587 (98.0)	602 (99.7)
Grade 1 or 2	555 (92.7)	563 (93.2)
Grade 3 or 4	193 (32.2)	191 (31.6)
Most common (>2% in TMC125 group) grade 3 and 4 laboratory abnormalities		
Increased pancreatic amylase	44 (7.5)	48 (7.9)
Increased triglycerides	41 (7.0)	26 (4.3)
Increased total cholesterol	34 (5.8)	25 (4.1)
Increased LDL-cholesterol	30 (5.2)	32 (5.4)
Decreased neutrophils	22 (3.7)	38 (6.3)
Increased glucose	15 (2.5)	12 (2.0)
Increased ALT	15 (2.5)	10 (1.7)
Increased AST	15 (2.5)	10 (1.7)

*DAIDS toxicity grading was used

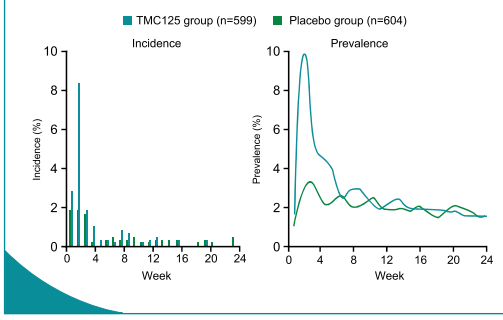
AEs of interest: rash

- **Overall incidence**
  - regardless of causality: 17% in TMC125 group vs 9.4% in placebo group (p=0.0001)
  - considered at least possibly related to study medication: 12.2% vs 4.8% in the TMC125 group versus placebo groups, respectively
- **In the TMC125 group**
  - **early onset:** median onset Day 12
  - **limited duration:** median duration 11 days
  - **low severity:** usually mild-to-moderate; 1.3% grade 3 and 0% grade 4
    - mostly maculopapular in nature; no rashes with mucosal involvement
  - **infrequently led to permanent discontinuation:** 2.2% of patients
    - most self-limiting with continued treatment
  - higher incidence in **women** (28.3% vs 15.8% in males), but no difference in severity or discontinuations between genders
  - no association with baseline **CD4** cell count
  - **no increased risk** in patients with a history of NNRTI-related rash

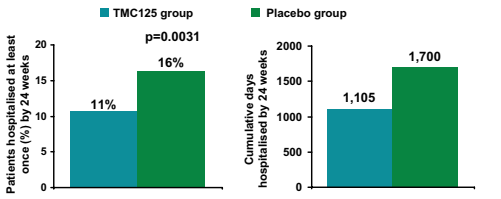
Lipid changes over time



Incidence and prevalence of rash (any type) by treatment group

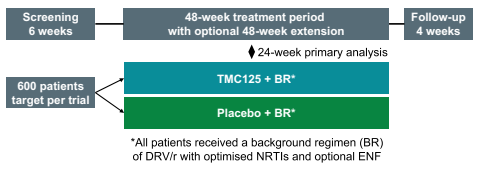


Hospitalisations



- Significantly fewer patients in the TMC125 group were hospitalised than in the placebo group by 24 weeks on treatment (64 vs 99 patients respectively; p=0.0031)
- 18 patients were hospitalised more than once in the TMC125 group vs 33 patients in the placebo group (p=0.03)

DUET study design and major inclusion criteria



*All patients received a background regimen (BR) of DRV/r with optimised NRTIs and optional ENF

- DUET-1 and -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 mutations,‡ 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; Tambuyzer L, et al. EHDRW 2007. Abstract 67

AEs of interest: nervous system*

- **Similar incidence to placebo:** 14.9% in TMC125 group vs 18.5% in placebo group (p=0.0896)
- **Low severity:** mostly grade 1 or 2, with grade 3 AEs reported in <2% of patients in both groups and no grade 4 AEs reported
- **Did not lead to discontinuation in the TMC125 group:** no patients in the TMC125 group and 1% of patients in the placebo group

Patients experiencing nervous system-related AEs, n (%)	TMC125 group (n=599)	Placebo group (n=604)
Grade 3	1 (0.3)	5 (1.6)
Grade 4	0	0
Most common (reported in ≥1% of patients in the TMC125 group)		
Headache	56 (9.3)	74 (12.3)
Dizziness	16 (2.7)	25 (4.1)
Somnolence	10 (1.7)	12 (2.0)

*Selected based on the nervous system events commonly associated with approved NNRTIs

Baseline characteristics and treatment duration

Parameter, % or median (range)		TMC125 group (n=599)	Placebo group (n=604)
Treatment duration at time of analysis (weeks)		30 (1–60)	29 (3–55)
Patient demographics	Male (%)	90	89
	Caucasian (%)	70	70
	Age	45 (18–77)	45 (18–72)
Disease characteristics	Viral load ($\log_{10}$ copies/mL)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
	Viral load >100,000 copies/mL	38	36
	CD4 cells (cells/mm^3)	99 (1.0–789)	109 (0.0–912)
	CD4 cells <50 cells/mm^3	36	35
	CDC category C (%)	58	59
	Hepatitis B/C co-infection	13	12
Patient history	Psychiatric symptoms (any type)	46	42
	NNRTI-associated rash	8	14
Prior ARV use	≥10 ARVs (%)	80	83

ARV = antiretroviral

AEs of interest: psychiatric disorders

- **Similar incidence to placebo:** 12.9% in TMC125 group vs 15.1% in placebo group (p=0.2803)
- **Low severity:** mostly grade 1 or 2, with grade 3 AEs reported in <2% of patients in both groups and no grade 4 AEs reported in the TMC125 group
- **Infrequently lead to discontinuation:** one patient (0.2%) in each group
- **No increased risk** in patients with a history of psychiatric disorders
- Abnormal dreams/nightmares in five patients (0.8%) in each group and no episodes of hallucinations, suicidal ideation or manic symptoms in the TMC125 group

Patients experiencing psychiatric-related AEs, n (%)	TMC125 group (n=599)	Placebo group (n=604)
Grade 3	1 (0.2)	8 (1.3)
Grade 4	0	1 (0.2)
Most common (reported in ≥1% of patients in the TMC125 group)		
Insomnia	33 (5.5)	40 (6.6)
Depression	18 (3.0)	30 (5.0)
Anxiety	15 (2.5)	18 (3.0)
Sleep disorder	7 (1.2)	4 (0.7)

Overview of AEs

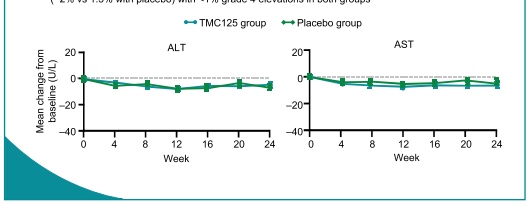
Parameter, n (%)	TMC125 group (n=599)	Placebo group (n=604)
Any AE (any cause)	554 (92.5)	559 (92.5)
Grade 3 AE	129 (21.5)	149 (24.7)
Grade 4 AE	43 (7.2)	54 (8.9)
Serious AE	79 (13.2)	113 (18.7)
Possibly related to study medication	14 (2.3)	15 (2.5)
Death (any cause)	8 (1.3)	15 (2.5)
Discontinuation due to AE	35 (5.8)	27 (4.5)
Most common AEs (>10% in either group, regardless of severity and causality)*		
Rash (any type)	102 (17.0)‡	57 (9.4)
Diarrhoea	90 (15.0)	123 (20.4)
Nausea	83 (13.9)	67 (11.1)
Headache	56 (9.3)	74 (12.3)

- AEs leading to death were not reported in more than one patient except for pneumonia and sepsis (n=2 each) in the placebo group
- None of the deaths in the TMC125 group were considered related to TMC125

*Excluding injection site reactions; ‡p=0.0001 vs placebo

Hepatic AEs and laboratory abnormalities

- **Hepatic AEs**
  - **similar incidence to placebo:** 5.3% in TMC125 group vs 5.1% in placebo group
  - **low severity:** mostly grade 1or 2
  - **infrequently led to discontinuation:** 0.7% of patients in both groups
  - **hepatitis co-infected patients:** Most hepatic AEs were grade 1 or 2. Grade 3 or 4 hepatic AEs reported with similar incidence in TMC125 and placebo groups (4.2% vs 4.4%, respectively)
- **ALT and AST laboratory abnormalities:** incidence of grade 3 ALT and AST elevations was low (~2% vs 1.3% with placebo) with <1% grade 4 elevations in both groups



Conclusions

- Safety and tolerability of TMC125 was generally comparable to placebo, except for the incidence of rash.
- Overall, most AEs were of low severity and infrequently led to discontinuation.
- Neuropsychiatric events were generally of low severity and similar between TMC125 and placebo groups.
- Rash, the only AE to occur more frequently with TMC125, was
  - generally mild-to-moderate
  - generally self-limited on continuing treatment
  - associated with low discontinuation.
- TMC125 was not associated with increases in laboratory abnormalities, including hepatic and lipid parameters.
- A significantly lower proportion of patients were hospitalised in the TMC125 versus placebo group.
- TMC125 provides a well-tolerated new option for treatment-experienced patients.

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DUET-1

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DUET-2

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