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Impact of TMC125, a next-generation NNRTI, on clinical outcomes (AIDS-defining illnesses and deaths): 24-week findings from a planned pooled analysis of the DUET studies

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Abstract

Objectives: To evaluate, at 24 weeks, differences in clinical outcome (i.e. AIDS-defining illnesses and deaths) between TMC125 (etravirine; ETR) plus background regimen (BR; darunavir/ritonavir, NRTI[s] and optional enfuvirtide [ENF]) and placebo plus BR in a pooled analysis of DUET-1 and DUET-2. These are two identical, ongoing, randomised, double-blind, placebo-controlled, Phase III trials, aiming to show superiority of TMC125 over placebo in HIV-1-infected, treatment-experienced patients. Efficacy and safety results from DUET have been reported recently.

Methods: In the DUET trials, AIDS-defining illnesses were identified using the adverse event (AE) preferred terms that appear as Category C illnesses in the 1993 revised classification system for HIV infection issued by the USA Centers for Disease Control (CDC). Deaths from any cause were counted. Data presented are part of the primary analysis. All patients were treated for at least 24 weeks or discontinued.

Results: 1,203 patients were analysed: 599 vs 604 in the TMC125 versus placebo groups. Baseline characteristics were comparable between arms. Overall results were 6.8% vs 3.7% for placebo plus BR vs TMC125 plus BR, respectively.

Table: Clinical endpoints (AIDS-defining illness or death)

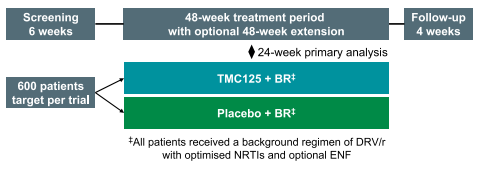
	TMC125, n (%) (n=599)	Placebo, n (%) (n=604)
Overall population		
Any AIDS-defining illness or death	**22 (3.7)***	**41 (6.8)**
CDC class A	2 (0.3)	4 (0.7)
CDC class B	0	5 (0.8)
CDC class C	20 (3.3)	32 (5.3)
Any AIDS-defining illness	**18 (3.0)**	**35 (5.8)**
Death	**8 (1.3)**	**15 (2.5)**
ENF *de novo*		
Any AIDS-defining illness or death	**5 (3.3)****	**4 (2.5)**
CDC class B	0	1 (0.6)
CDC class C	5 (3.3)	3 (1.9)
Any AIDS-defining illness	**4 (2.6)**	**3 (1.9)**
Death	**2 (1.3)**	**2 (1.3)**
ENF not using/re-using *de novo*		
Any AIDS-defining illness or death	**17 (3.8)*****	**37 (8.3)**
CDC class A	2 (0.4)	4 (0.9)
CDC class B	0	4 (0.9)
CDC class C	15 (3.4)	29 (6.5)
Any AIDS-defining illness	**14 (3.1)**	**32 (7.2)**
Death	**6 (1.3)**	**13 (2.9)**

There was a statistically significant reduction in these events for patients receiving TMC125 over placebo in the subgroup that did not use ENF *de novo* in the BR (p=0.0051)
*p=0.4419; **p=0.6892; ***p=0.0051

Conclusions: At Week 24, TMC125 plus BR provided a reduction in AIDS-defining illnesses and/or deaths versus placebo plus BR (statistically significant for patients not using ENF *de novo*). DUET trials are planned to continue until 96 weeks.

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

DUET study design and major inclusion criteria



‡All patients received a background regimen of DRV/r with optimised NRTIs and optional ENF

- 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 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)

Assessment of clinical outcomes (AIDS-defining illnesses and deaths)

- At the time of this analysis, all patients were treated for ≥24 weeks or had discontinued
- Analyses use the ITT patient population and statistical testing was done on the overall population and according to ENF use (re-use, no use, or use for the first time [*de novo*])
- AIDS-defining illnesses were identified using the reported AE terms that appear as Category C illnesses in the 1993 revised classification system for HIV infection issued by the US CDC
  - AEs were selected from a pre-defined list prior to database lock
- AEs were not reviewed by an independent committee in this analysis, but certification by an independent expert adjudication panel is ongoing
- All deaths were included in the 24-week analysis
- All hospital admissions in the 24-week analysis were recorded and evaluated

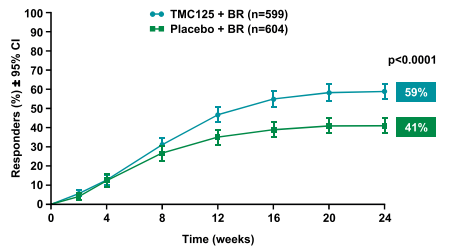
ITT = intent-to-treat

Baseline characteristics from pooled DUET-1 and DUET-2

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
Prior ARV use	10–15 ARVs (%)	66	64
	DRV/r (%)	4	5
Detectable mutations	≥2 NNRTI mutations† (%)	66	66
	≥4 primary PI mutations (%)	62	63
Activity of BR	Active background agents§ = 0 (%)	17	16
	Active background agents§ = 1 (%)	36	39

†From extended list of NNRTI mutations (Tambuyzer et al. Abstract 67 EHDRW 2007)
§Assessed by phenotypic sensitivity score (PSS); ARV = antiretroviral

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



CI = confidence interval; TLOVR = time to loss of virologic response imputation algorithm

Overview of AEs (regardless of causality)

Parameter, %		TMC125 + BR (n=599)	Placebo + BR (n=604)
Any AE (any cause)		93	93
Grade 3/4 AE		25	27
Discontinuation due to AE		6	4
Serious AE		13	19
Death (any cause), % (n)		1.3 (8)‡	2.5 (15)
Most common AEs§	Rash (any type)	17	9
	Diarrhea	15	20
	Nausea	14	11
	Headache	9	12
AEs of interest	Nervous system disorders	15	19
	Psychiatric disorders	13	15
	Hepatic AEs	5	5

- Most cases of rash were mild to moderate and resolved with continued therapy
- There were no consistent or clinically relevant trends in laboratory, vital signs or ECG data
- The profile of laboratory abnormalities, including hepatic and lipid parameters, was generally similar between the TMC125 and placebo groups

‡No deaths in the TMC125 group were considered related to trial medication
§In >10% patients in either group, excluding injection site reactions; †p=0.0001 vs placebo

Summary of clinical outcomes‡

	TMC125 group, n (%) (n=599)	Placebo group, n (%) (n=604)
Overall population		
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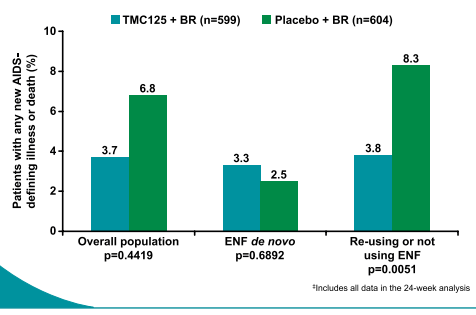
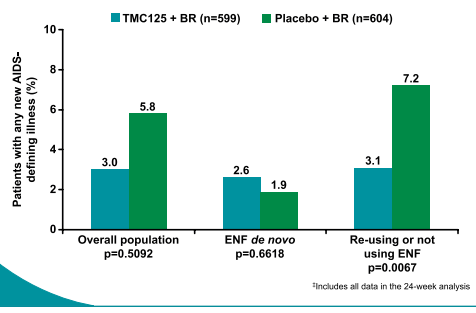
‡Includes all data in the 24-week analysis; *p=0.4419; **p=0.6892; ***p=0.0051

Proportion of patients with any new AIDS-defining illness or death‡



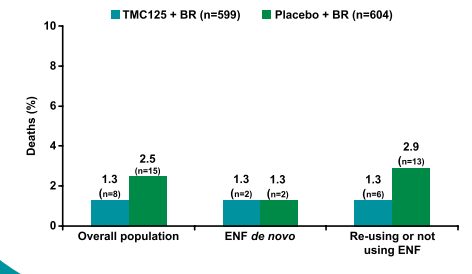
‡Includes all data in the 24-week analysis

Proportion of patients with any new AIDS-defining illness‡



‡Includes all data in the 24-week analysis

Proportion of deaths‡



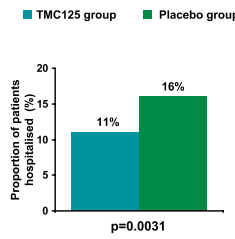
‡Includes all data in the 24-week analysis

Description of deaths‡

- 33 patients died during the course of the DUET trials in the Week 24 analysis
  - 10 patients died during screening
  - 23 patients died due to an AE in the treatment period (TMC125, n=8; placebo, n=15)
- AEs leading to death were mainly associated with disease progression or HIV-related complications
  - the most common fatal AEs were related to infections and infestations (TMC125, n=5; placebo, n=8)
  - in the TMC125 group, three patients experienced fatal SAEs considered doubtfully related to TMC125 (renal impairment, respiratory tract infection or *Mycobacterium avium* complex infection)
  - in the placebo group, one patient had a fatal SAE (acute renal failure) possibly related and two patients had a fatal SAE (pyrexia in one patient; pneumonia and sepsis in one patient) doubtfully related to treatment

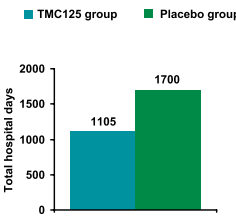
‡Includes all data in the 24-week analysis; SAE = serious adverse event

Proportion of patients hospitalised by Week 24



- Significantly fewer patients in the TMC125 group were hospitalised than in the placebo group (p=0.0031)

Total hospital days by Week 24



- Total number of hospital days was less in the TMC125 group compared with placebo
- 18 patients were hospitalised more than once in the TMC125 group versus 33 patients in the placebo group (p=0.03)

Conclusions

- In the pooled DUET-1 and -2 analysis, three out of five patients receiving TMC125 achieved <50 copies/mL undetectable viral load
  - 59% with TMC125 plus BR vs 41% with placebo plus BR achieved <50 copies/mL (p<0.0001).
- Most AEs were mild-to-moderate and infrequently led to discontinuation
  - some patients experienced mild-to-moderate rash
  - TMC125 was not associated with neuropsychiatric, hepatic or lipid toxicity.
- There was a consistent trend for fewer clinical endpoints (any new AIDS-defining illnesses and/or deaths) in the TMC125 group
  - this trend reached statistical significance in patients not using/re-using ENF.
- Additionally, there were statistically significantly fewer hospitalisations in patients receiving TMC125.
- In addition to beneficial effects on surrogate markers (viral load and CD4 cell count), TMC125 was associated with a lower rate of clinical endpoints in the DUET trials.

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DUET-1
Argentina: HA Ariza, J Benetucci, P Cahn, LM Calanni, LI Cassetti, J Corral, DO David, A Krolewiecki, MH Losso, P Patterson, RA Teijeiro; **Brazil:** CA da Cunha, B Grinsztejn, EG Kallas, EM Netto, JV Madruga, JH Pilotto, M Schechter, J Suleiman, A Timerman; **Chile:** J Ballesteros, R Northland; **Costa Rica:** AA Alvilés Montoya, G Herrera Martinez, A Solano Chinchilla; **France:** M Dupon, C Katlama, JM Livrozet, P Morlat, G Pialoux, C Piketty, I Poizot-Martin; **Mexico:** J Andrade-Villanueva, G Reyes-Terán, J Sierra-Madero; **Panama:** A Canton, A Rodriguez, N Sosa; **Puerto Rico:** JO Morales Ramirez, JL Santana Bagur, R Soto-Malave; **Thailand:** T Anekthananon, P Mootsikapun, K Ruxrungtham; **USA:** M Albrecht, N Bellos, R Bolan, P Brachman, C Brinson, F Cruickshank, R Elion, WJ Fessel, R Haubrich, T Hawkins, S Hodder, P Hutcherson, T Jefferson, H Katner, C Kinder, M Kozal, J Lalezari, J Leider, T Mills, D McDonough, K Mounzer, J Nadler, D Norris, W O'Brien, G Pierone, K Raben, B Rashbaum, M Rawlings, B Rodwick, P Ruane, J Sampson, S Schrader, A Scribner, M Sension, D Sweet, B Wade, D Wheeler, A Wilkin, T Wills, M Wohlfeiler, K Workowski.

DUET-2
Australia: J Chuah, D Cooper, B Eu, J Hoy, C Workman; **Belgium:** N Clumeck, R Colebunders, M Moutschen; **Canada:** J Gill, K Gough, P Junod, D Kilby, J Montaner, A Rachlis, B Trottier, CM Tsoukas, SL Walmsley; **France:** C Arvieux, L Cotte, JF Delfraissy, PM Girard, C Katlama, B Marchou, JM Molina, D Vittecoq, Y Yazdanpanah, P Yeni; **Germany:** K Arastéh, S Esser, G Fätkenheuer, H Gellermann, K Göbels, FD Goebel, H Jäger, A Moll, JK Rockstroh, D Schuster, S Staszewski, A Stoehr; **Italy:** A Antinori, G Carosi, G Di Perri, R Esposito, A Lazzarin, F Mazzotta, G Pagano, E Raise, S Rusconi, L Sighinolfi, F Suter; **The Netherlands:** PHJ Frissen, JM Prins, BJA Rijnders; **Poland:** A Horban; **Portugal:** F Antunes, M Miranda, J Vera; **Spain:** B Clotet, P Domingo, G Garcia, J González-Lahoz, J López-Aldeguer, D Podzamczer; **UK:** P Easterbrook, M Fisher, C Orkin, E Wilkins; **USA:** B Barnett, J Baxter, D Berger, C Borkert, T Campell, C Cohen, M Conant, J Ernst, C Farthing, T File, M Frank, JE Gallant, AE Greenberg, C Hicks, DT Jayaweera, S Kerkar, N Markowitz, C Martorell, C McDonald, D McMahon, M Mogyoros, RA Myers Jr, G Richmond, K Sathasivam, S Schneider, H Schrager, P Shalit, FP Siegal, L Sloan, K Smith, S Smith, P Tebas, LS Tkatch, W Towner.

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