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TMC125 safety and tolerability in treatment-experienced hepatitis B or C coinfected patients in DUET-1 and DUET-2

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Abstract

Background: DUET-1 and DUET-2 are ongoing, randomized, double-blind, placebo-controlled trials of identical design which investigate TMC125 (etravirine; ETR) in treatment-experienced, HIV-1-infected patients. We report safety results by baseline hepatitis coinfection status from a planned 24-week pooled analysis.

Methods: Patients with documented (historical data and/or viral genotype) NNRTI resistance and with ≥3 primary protease inhibitor (PI) mutations on stable virologically failing treatment were randomized to TMC125 200mg or placebo bid, each administered with darunavir/ritonavir, optimized NRTIs +/– enfuvirtide. To be eligible, patients coinfected with chronic hepatitis B or C (HBV/HCV) had to be clinically stable with aspartate aminotransferase/alanine aminotransferase (AST/ALT) <5x upper limit of normal. Coinfection status was determined by positive HbsAg or positive HCV RNA. Adverse events (AEs) and laboratory parameters were analyzed based on baseline hepatitis coinfection status.

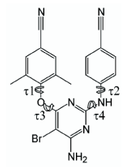
Results: Among 1130 patients included in the analysis, 140 (12.4%) were coinfected with hepatitis B and/or C; there were no differences in coinfection status between treatment groups. With the exception of rash, the overall incidence of AEs was generally similar between treatment groups, irrespective of coinfection status. Most AEs were mild-to-moderate in severity. The incidence of grade 3/4 hepatic AEs, serious hepatic AEs and hepatic AEs leading to discontinuation among coinfected patients was comparable between the treatment groups. In both treatment groups, grade 3/4 AST/ALT elevations were more frequent in those who were coinfected; differences between TMC125 and placebo were small.

Conclusions: Consistent with the underlying chronic hepatitis coinfection, hepatic AEs and elevated hepatic parameters were more frequent in coinfected patients compared with non-coinfected patients. The incidence and severity of hepatic AEs with TMC125 were generally similar to placebo, irrespective of hepatitis coinfection status. TMC125 does not appear to increase hepatic toxicity in patients with hepatitis coinfection.

Note: abstract has been modified.

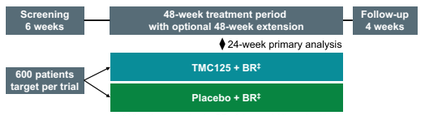
Introduction

- TMC125 is a next-generation NNRTI for the treatment of HIV-1 infection designed to have a high genetic barrier to the development of resistance
- Proof-of-principle studies have demonstrated significant antiviral activity in both therapy-naïve and therapy-experienced patients[1,2]
- A pharmacokinetic study in HIV-negative volunteers with mild-to-moderate hepatic impairment showed no TMC125 dose adjustments are necessary in this sub-population[3]
- DUET-1 and DUET-2 were Phase III, double-blind, placebo-controlled trials of TMC125 + background regimen (BR) in treatment-experienced HIV-1-infected patients[4,5]
  - 59% of TMC125 patients reached undetectable viral load (<50 copies/mL) at 24 weeks vs 41% of placebo patients
  - The safety and tolerability of TMC125 was generally similar to placebo
- This analysis examined the safety and tolerability of TMC125 in HIV-1-infected patients coinfected with hepatitis B and/or C in the pooled DUET studies



1. Gazzard B, et al. AIDS 2003;17:49–54
2. Gruzdev B, et al. AIDS 2003;17:2487–94; 3. Schöller-Gyüre M, et al. ICAAC 2007. Abstract 1428
4. Madruga J, et al. Lancet 2007;370:29–38; 5. Lazzarin A, et al. Lancet 2007;370:39–48

DUET study design and major inclusion criteria



‡All patients received a BR of darunavir/ritonavir with optimized NRTIs and optional enfuvirtide

- DUET-1 and DUET-2 differed only in geographic location; pooled analysis was prespecified
- Major inclusion criteria
  - HIV-1 infection
  - Plasma viral load >5000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
  - ≥1 NNRTI mutations,§ at screening or in documented historic 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

DUET hepatitis coinfection inclusion/exclusion criteria

- Inclusion
  - Hepatitis B confirmed by positive HBV sAg
  - Hepatitis C confirmed by positive HCV Ab and confirmatory qualitative HCV RNA
    - In immunocompromised patients with CD4 cell count <100 cells and negative HCV Ab, qualitative HCV RNA was assessed
  - HIV-1/hepatitis coinfected patients were required to have
    - AST and/or ALT <5 x ULN
    - Clinically stable disease
    - No expected antihepatitis treatment during the trial period
- Exclusion
  - Clinic or laboratory evidence of significantly decreased hepatic function or decompensation, irrespective of liver enzyme levels (International Normalized Ratio [INR] >1.5 or albumin <30 g/L or bilirubin >2.5 x ULN)

ULN = upper limit of normal

Baseline characteristics and treatment duration: total population

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 >100000 copies/mL (%)	38	36
	CD4 cells (cells/mm³)	99 (1.0–789)	109 (0.0–912)
	CDC category C (%)	58	59
Patient history	Psychiatric symptoms (any type)	46	42
	NNRTI-associated rash	8	14
Prior ARV use	≥10 ARVs (%)	80	83
Number of hepatitis B/C coinfected patients n, (%)		72 (13)	68 (12)
Confirmed hepatitis B infection, n		41	38
Confirmed hepatitis C infection, n		30	35

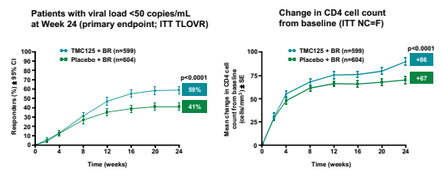
ARVs = antiretrovirals

Baseline characteristics: population with hepatitis data

Parameter, % or median (range)		Coinfected TMC125 (n=72)	Coinfected Placebo (n=68)	Non-coinfected TMC125 (n=494)	Non-coinfected Placebo (n=496)
Patient demographics	Male (%)	93	87	89	89
	Caucasian (%)	69 (N=61)	80 (N=59)	70 (N=442)	69 (N=443)
	Age	44 (31–60)	43 (20–61)	46 (18–77)	46 (18–72)
Disease characteristics	Viral load (log_{10} copies/mL)	4.8 (3.3–6.2)	4.9 (2.2–5.9)	4.8 (2.7–6.8)	4.8 (2.4–6.3)
	Viral load ≥100000 copies/mL (%)	35	38	38	34
	CD4 cells, cells/mm³	92.5 (1–666)	101.5 (1–801)	119.5 (1–789)	121.5 (0–912)
	CDC category C (%)	67	59	57	59

n = total population; N = number of patients with data available

Pooled DUET efficacy results



ITT = intent-to-treat population; TLOVR = time-to-loss of virologic response imputation algorithm
NC=F = noncompleter equals failure imputation algorithm
CI = confidence interval; SE = standard error

Overview of AEs: total population

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

AE = adverse event; BR = background regimen
‡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

Frequency of AEs by coinfection status

Incidence, %	Coinfected TMC125 (n=72)	Coinfected Placebo (n=68)	Coinfected OR (95% CI)	Non-coinfected TMC125 (n=494)	Non-coinfected Placebo (n=496)	Non-coinfected OR (95% CI)
Any AE (any cause)	93	94	1.19 (0.31–4.65)	92	92	1.03 (0.65–1.64)
Any grade 3 or 4 AE	24	35	1.76 (0.84–3.69)	24	26	1.12 (0.84–1.49)
Discontinuation due to AE	7	7	1.06 (0.29–3.85)	5	4	0.73 (0.40–1.31)
Any serious AE	18	22	1.28 (0.56–2.95)	12	18	1.58 (1.11–2.25)
Deaths (any cause)	3	3	1.06 (0.15–7.75)	1	2	2.22 (0.77–6.43)

OR = odds ratio of placebo over TMC125; CI = confidence interval; AE = adverse event

AEs of specific interest analyzed by coinfection status

Incidence, %	Coinfected TMC125 (n=72)	Coinfected Placebo (n=68)	Coinfected OR (95% CI)	Non-coinfected TMC125 (n=494)	Non-coinfected Placebo (n=496)	Non-coinfected OR (95% CI)
Rash (any type)	17	9	0.48 (0.17–1.37)	17	9	0.49 (0.34–0.72)
Nervous system	7	12	1.79 (0.55–5.76)	16	20	1.33 (0.96–1.84)
Psychiatric	14	18	1.33 (0.53–3.31)	13	14	1.16 (0.81–1.68)

OR = odds ratio of placebo over TMC125; CI = confidence interval

Hepatic AEs by coinfection status

Incidence, %	Coinfected TMC125 (n=72)	Coinfected Placebo (n=68)	Coinfected OR (95% CI)	Non-coinfected TMC125 (n=494)	Non-coinfected Placebo (n=496)	Non-coinfected OR (95% CI)
Any hepatic AE	6	12	2.27 (0.65–7.91)	5	5	1.19 (0.66–2.12)
Grade 3 or 4 hepatic AEs	4	6	1.44 (0.31–6.67)	2	2	0.90 (0.38–2.15)
Discontinuation due to hepatic AEs	1	3	2.15 (0.19–24.28)	1	<1	0.66 (0.11–3.98)

OR = odds ratio of placebo over TMC125; CI = confidence interval; AE = adverse event

Hepatic grade 3 or 4 laboratory parameters by coinfection status

Incidence, %	Coinfected TMC125 (n=72)	Coinfected Placebo (n=68)	Coinfected OR (95% CI)	Non-coinfected TMC125 (n=494)	Non-coinfected Placebo (n=496)	Non-coinfected OR (95% CI)
Elevated AST	6	4	0.78 (0.17–3.64)	2	1	0.59 (0.21–1.64)
Elevated ALT	7	6	0.84 (0.22–3.26)	2	1	0.66 (0.23–1.87)
Hyper-bilirubinemia	6	1.0	0.25 (0.03–2.33)	0.6	0.4	0.66 (0.11–3.98)
Elevated alkaline phosphatase	0	1.0	Not calculated†	0.2	1.2	6.87 (0.81–58.65)

OR = odds ratio of placebo over TMC125; CI = confidence interval
AST = aspartate aminotransferase; ALT = alanine aminotransferase
†There were insufficient numbers of patients to calculate OR

Conclusions

- Irrespective of coinfection status, the safety and tolerability of TMC125 was generally comparable to placebo.
- Consistent with the underlying chronic hepatitis coinfection, in both treatment groups, hepatic AEs and elevated hepatic parameters were more frequent in HIV patients coinfected with hepatitis compared to those HIV patients not coinfected with hepatitis.
- In both treatment groups, grade 3 and 4 AST/ALT elevations were more frequent in HIV-1/hepatitis coinfected patients, but there were no significant differences between TMC125 and placebo.
- The incidence of grade 3 and 4 hepatic AEs was similar between treatment groups, regardless of coinfection status
  - Discontinuations due to hepatic AEs were infrequent and comparable between the placebo and TMC125 groups.
- TMC125 was not associated with hepatic toxicity in hepatitis B/C HIV-1 coinfected patients and provides a well-tolerated new option for treatment-experienced patients.

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DUET-1
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