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Lipid profiles of TMC278 and efavirenz in treatment-naïve, HIV-1-infected patients: pooled Week 48 data from the randomized, double-blind, Phase III ECHO and THRIVE trials

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Introduction

- TMC278 (rilpivirine), an investigational NNRTI, had non-inferior efficacy to efavirenz (EFV) in treatment-naïve patients in the Week 48 primary analysis of two Phase III, double-blind trials, ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725).[1]
- The aim of the current analysis was to compare, under fasted conditions, abnormalities and changes in lipid parameters with TMC278 versus EFV over 48 weeks using pooled Phase III data from the ECHO and THRIVE trials.

Methods

Study design

- ECHO and THRIVE are ongoing, global, Phase III, double-blind, double-dummy trials in treatment-naïve, HIV-1-infected adults randomized to receive TMC278 25 mg qd or EFV 600 mg qd, plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) (ECHO) or investigator-selected TDF/FTC, zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC) (THRIVE).[1]

Study assessments and endpoints

- The use of lipid-lowering drugs at baseline or post-baseline was very low, therefore it was not taken into account in the analysis.
- Changes from baseline in fasting total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides were assessed over 48 weeks in the intent-to-treat (ITT) analysis.
- Baseline-corrected values for the proportion of patients with at least one lipid value outside (above or below) the National Cholesterol Education Program (NCEP) cut-off value at any timepoint were calculated. Cut-off values were: total cholesterol 200 mg/dL; LDL-C 130 mg/dL; HDL-C: males 40 mg/dL and females 50 mg/dL, and triglycerides 150 mg/dL.
- Treatment-emergent, lipid-related abnormalities were evaluated and graded according to Division of AIDS (DAIDS) criteria.[2]
- The change from baseline to Week 48 in Framingham Coronary Heart Disease (CHD) relative-risk score (10-year risk) for LDL-C was calculated.

Results

Baseline characteristics

- Overall (N=1368), baseline patient demographics and disease characteristics were similar between groups (**Table 1**).

Table 1. Patient demographics and baseline disease characteristics.

Parameter	TMC278 N=686	EFV N=682
Demographics		
Female, %	24.5	23.9
Median age, years (range)	36 (18–78)	36 (19–69)
Race, %		
Caucasian/White	61.4	60.1
Black/African-American	24.1	22.9
Asian	11.4	14.2
Other races/not allowed to ask	3.1	2.8
Smokers, %	35.9	32.7
Disease characteristics		
Median $\log_{10}$ viral load, copies/mL (min–max)	5.0 (2–7)	5.0 (3–7)
Baseline viral load >100,000 copies/mL, %	46.4	51.6
Median CD4 cell count, cells/mm^3 (min–max)	249 (1–888)	260 (1–1137)
Hepatitis B and/or C co-infection, %	7.3	9.5
Use of lipid-lowering drugs, %	1.6	1.2

- Baseline use of lipid-modifying therapies was infrequent, and background regimens were balanced between treatment groups: TDF/FTC 80%; AZT/3TC 15% and ABC/3TC 5%.

Baseline lipid parameters

- Baseline lipid parameters were similar between the TMC278 and EFV treatment groups (**Table 2**).

Table 2. Baseline lipid parameters (fasted).

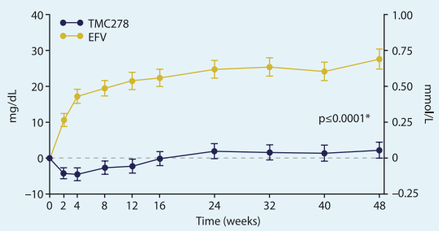
Mean (SD) lipid parameter	TMC278 N=686 mg/dL	TMC278 N=686 mmol/L	EFV N=682 mg/dL	EFV N=682 mmol/L
Total cholesterol	160.9 (34.5)	4.2 (0.9)	161.0 (36.4)	4.2 (0.9)
LDL-C	96.1 (29.7)	2.5 (0.8)	95.6 (32.2)	2.5 (0.8)
HDL-C	41.2 (12.5)	1.1 (0.3)	39.7 (11.4)	1.0 (0.3)
Total cholesterol/HDL-C ratio	4.2 (1.5)		4.3 (1.3)	
Triglycerides	124.0 (80.6)	1.4 (0.9)	133.1 (94.7)	1.5 (1.1)

The number of observations for each parameter did not always equal the total number of patients in each group due to test results not being available for a small number of patients;
SD = standard deviation

Changes in fasted lipid parameters from baseline to Week 48

- The mean (SD) increase from baseline to Week 48 in total cholesterol was significantly lower with TMC278 than EFV: 2 (28) vs 27 (35) mg/dL, (0.05 [0.71] vs 0.71 [0.90] mmol/L), respectively (p≤0.0001) (**Figure 1**).

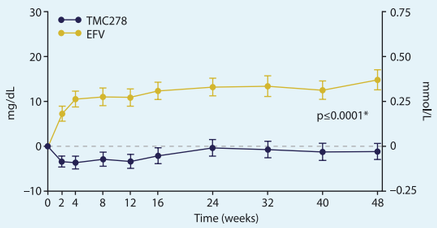
Figure 1. Mean (±95% confidence interval [CI]) change in total cholesterol from baseline to Week 48.



*p value versus EFV at Week 48 (non-parametric Wilcoxon rank-sum test, post-hoc analysis)

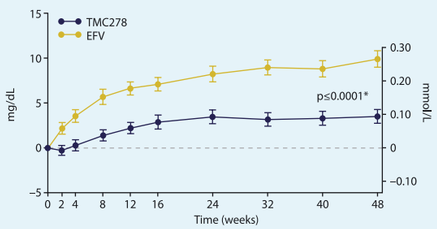
- There was an increase from baseline to Week 48 in mean (SD) LDL-C levels for EFV: 14 (28) mg/dL (0.37 [0.73] mmol/L), but a small mean decrease from baseline for TMC278: –1 (23) mg/dL (–0.03 [0.60] mmol/L) (p≤0.0001 TMC278 versus EFV) (**Figure 2**).
- The mean (SD) increase from baseline at Week 48 in HDL-C was significantly lower with TMC278 than EFV: 3 (9) vs 10 (11) mg/dL, (0.09 [0.24] vs 0.26 [0.27] mmol/L), respectively (p≤0.0001 TMC278 versus EFV) (**Figure 3**), with no difference between groups in the change in ratio of total cholesterol/HDL-C (–0.25 vs –0.26) (**Figure 4**).
- At Week 48, there was a mean (SD) increase from baseline in triglyceride levels for EFV: 13 (139) mg/dL (0.15 [1.6] mmol/L), and a small mean decrease for TMC278: –7 (77) mg/dL (–0.08 [0.87] mmol/L) (p≤0.0001 TMC278 versus EFV) (**Figure 5**).

Figure 2. Mean (±95% CI) change in LDL-C from baseline to Week 48.



*p value versus EFV at Week 48 (non-parametric Wilcoxon rank-sum test, post-hoc analysis)

Figure 3. Mean (±95% CI) change in HDL-C from baseline to Week 48.



*p value versus EFV at Week 48 (non-parametric Wilcoxon rank-sum test, post-hoc analysis)

Figure 4. Mean (±95% CI) change in total cholesterol/HDL-C ratio from baseline to Week 48.

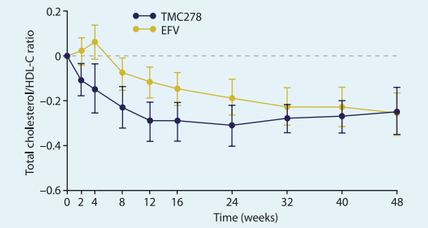
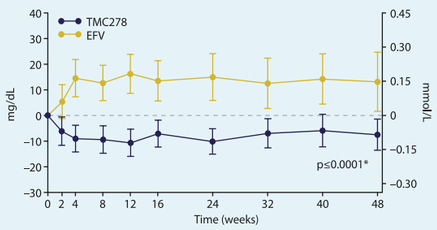


Figure 5. Mean (±95% CI) change in triglycerides from baseline to Week 48.



*p value versus EFV at Week 48 (non-parametric Wilcoxon rank-sum test, post-hoc analysis)

Proportion of patients with lipid values outside NCEP cut-offs

- Baseline-corrected values for proportions of patients with at least one lipid value outside NCEP cut-offs at any timepoint are shown in **Table 3**.

Table 3. Baseline-corrected proportions of patients with at least one lipid value above or below NCEP cut-offs.*

Lipid parameter, n/N (%)	TMC278	EFV	p value†
Total cholesterol (above)	107/599 (18)	267/580 (46)	<0.0001
LDL-C (above)	103/602 (17)	218/580 (38)	<0.0001
HDL-C (below)‡	149/270 (55)	97/224 (43)	0.0089
Triglycerides (above)	175/523 (33)	249/496 (50)	<0.0001
HDL-C males (below)‡	118/216 (55)	80/183 (44)	0.0349
HDL-C females (below)‡	31/54 (57)	17/41 (41)	0.1494

*Patients included are those whose lipid parameters were within NCEP cut-offs at baseline; †TMC278 vs EFV, Fisher's exact test, post-hoc analysis; ‡Patients were included even if they had one value below the cut-off value

Changes in fasted lipid parameters from baseline to Week 48 by N(t)RTI background regimen

- Changes from baseline to Week 48 in total cholesterol, LDL-C, triglycerides and HDL-C appeared higher in the EFV group than in the TMC278 group when results were analyzed according to N(t)RTI background regimen (**Table 4**). The exception was triglycerides in patients receiving an AZT/3TC background for whom changes were comparable between treatment groups.
- The differences between treatment groups were more apparent in patients receiving TDF/FTC.

Table 4. Mean change from baseline to Week 48 in lipid parameters (fasted) by N(t)RTI background regimen.

Mean (SD) lipid parameter, mg/dL	ABC/3TC TMC278 n=31	ABC/3TC EFV n=30	AZT/3TC TMC278 n=95	AZT/3TC EFV n=86	TDF/FTC TMC278 n=472	TDF/FTC EFV n=459
Total cholesterol	16.9 (27.7)	40 (43.6)	8.7 (29)	32.2 (38.3)	–0.4 (26.8)	25.7 (33.1)
LDL-C	5.8 (27.3)	22.3 (38.6)	1.7 (25.1)	17.4 (37.3)	–2.1 (22.4)	13.3 (25.4)
HDL-C	7.2 (6.1)	10.7 (10.4)	4.9 (9.7)	11.4 (12.8)	2.9 (9.2)	9.5 (10.2)
Triglycerides	13.2 (102.3)	43.3 (139.9)	11.8 (66)	9.4 (96.3)	–12.4 (76)	11.7 (145.2)

The number of observations for each parameter did not always equal the total number of patients in each subgroup due to test results not being available for a small number of patients

Treatment-emergent lipid abnormalities

- The incidence of all grades and grades 3 or 4 treatment-emergent lipid abnormalities (fasted values) was significantly lower in the TMC278 group than the EFV group (**Table 5**).

Discontinuations, use of lipid-lowering drugs and CHD risk

- Treatment-emergent dyslipidemia did not lead to discontinuation in either treatment group.
- The use of lipid-lowering drugs during the studies was low for both groups but lowest for the TMC278 group (2%; 15/686 patients) versus 4% in the EFV group (27/682 patients).
- Change from baseline to Week 48 in Framingham CHD relative-risk score (10-year risk) for LDL-C was the same in both treatment groups (–0.09) (note: Framingham CHD relative-risk score has not been validated in HIV-infected patients).

Table 5. Lipid-related, treatment-emergent abnormalities.

Laboratory parameter abnormality (fasted), %	TMC278 N'=685	EFV N'=668*	p value†
		All grades	
Total cholesterol	19	47	<0.0001
LDL-C	18	39	<0.0001
Triglycerides	2	4	0.0167
		Grades 3 or 4‡	
Total cholesterol	0.1	3	<0.0001
LDL-C	1	4	<0.0001
Triglycerides	0.3	2	0.0011

*N'=665 for LDL-C; †TMC278 vs EFV, Fisher's exact test, post-hoc analysis; ‡Grade 4 not applicable for total cholesterol and LDL-C according to DAIDS grading scale[2]

Conclusions

- TMC278 produced minimal changes in total cholesterol, LDL-C and triglyceride levels from baseline through 48 weeks of treatment. There was no relevant difference between treatment groups in change in ratio of total cholesterol/HDL-C.
- Beginning early in treatment, there were significantly greater increases in total cholesterol, LDL-C, triglycerides and HDL-C in the EFV group than in the TMC278 group, and the differences were sustained over 48 weeks.
- Treatment-emergent lipid abnormalities occurred at a significantly higher incidence in the EFV group than in the TMC278 group.
- There was no difference in change from baseline to Week 48 in Framingham CHD relative-risk score between the two treatment groups.
- A once-daily single-tablet regimen of TMC278 and TDF/FTC is under development.

References

1. Cohen C, et al. XVIIIth International AIDS Conference, Vienna, Austria, 18–23 July 2010. Abstract THLBB206.
2. Division of Acquired Immune Deficiency Syndrome (DAIDS) table for grading the severity of adult and pediatric adverse events. Version December 28, 2004.

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