Pooled Week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomised, Phase III trials comparing TMC278 versus efavirenz in treatment-naïve, HIV-1-infected patients

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Background

- **TMC278 (rilpivirine), a new NNRTI, has**
  - **potent anti-HIV-1 activity (EC_{50} = 0.3ng/mL)[1]**
  - **no teratogenicity in preclinical studies[2]**
  - **half-life of ≈ 45 hours[3]**
- **Phase IIb study[4] in treatment-naïve, HIV-1 patients showed TMC278 25mg once daily (qd) had**
  - **sustained efficacy similar to TMC278 75mg or 150mg qd or EFV 600mg qd**
  - **generally better tolerability than EFV**

[1]Azijn H, et al. AAC 2010;54:718–27
[2]Desmidt M, et al. EACS 2009. Abstract PE7.1/4
[3]Goebel F, et al. AIDS 2006;20:1721–6
[4]Pozniak A, et al. AIDS. 2010;24:55–65

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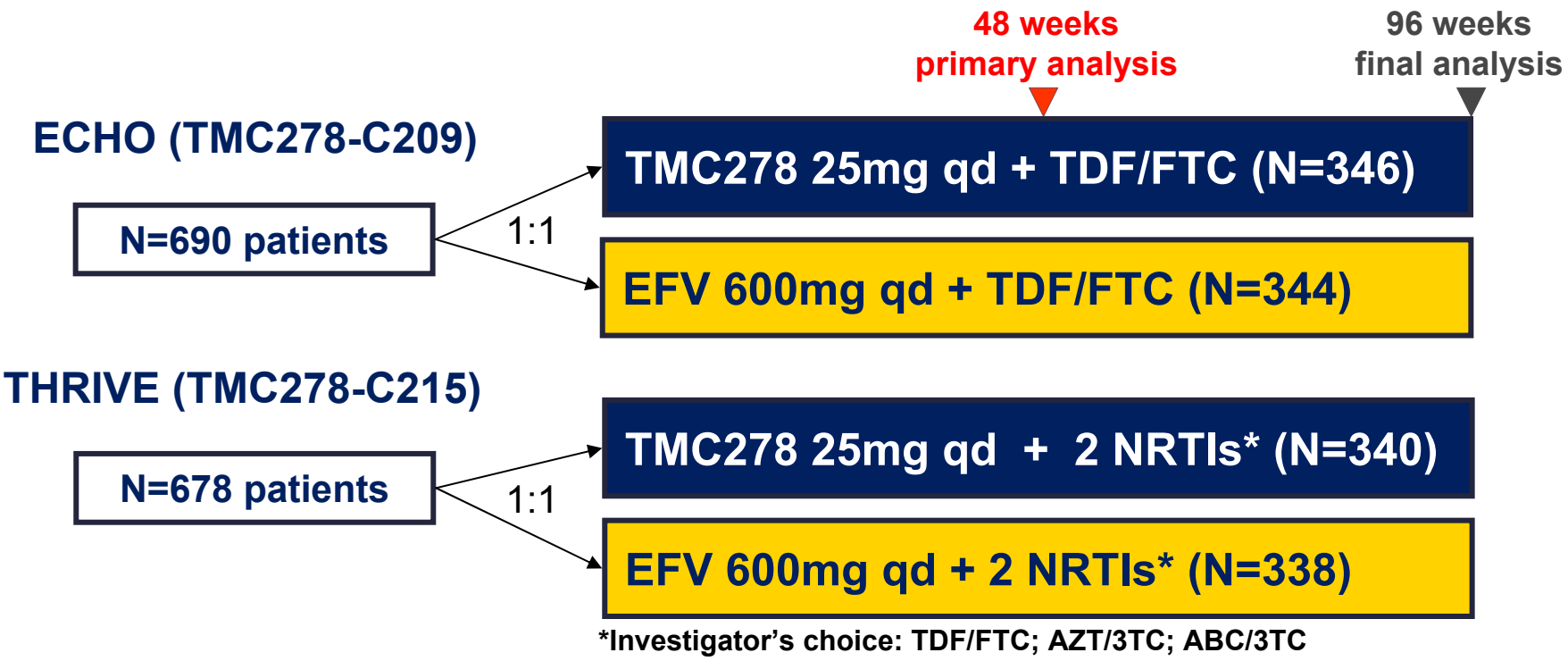
ECHO and THRIVE: Double-Blind trial designs



*Investigator's choice: TDF/FTC; AZT/3TC; ABC/3TC

- **Main inclusion criteria: viral load (VL) ≥ 5000 c/mL; no NNRTI RAMs†; sensitivity to the NRTIs‡**
- **Primary objective: demonstrate non-inferiority (12% margin) vs. EFV in confirmed virologic response (VL <50 c/mL, ITT-TLOVR) at Week 48**
- **Stratification factors: screening VL and NRTI background (THRIVE only)**

†From 39 NNRTI RAMs based on list of 44[1]
‡Determined using virco®TYPE HIV-1 test
ITT = intent-to-treat; TLOVR = time-to-loss of virologic response
Pooled analyses were preplanned

[1]Tambuyzer L et al. Antivir Ther 2009;14:103–9
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Pooled ECHO and THRIVE: demographics and baseline characteristics

Baseline parameter	TMC278 N=686	EFV N=682
Female, %	**25**	24
Median age, years	**36**	36
Race, %		
Caucasian	**61**	60
Black	**24**	23
Asian	**11**	14
Other races/not allowed to ask	**3**	3
Median $\log_{10}$ VL, copies/mL (min–max)	**5 (2–7)**	5 (3–7)
Baseline VL copies/mL, %		
>100,000	**46**	52
Median CD4 cells/mm^3 (min–max)	**249 (1–888)**	260 (1–1,137)
Hepatitis B or C co-infection, %	**7**	9

- **Demographics and baseline characteristics were well-balanced between treatment groups within each trial**
- **Background regimen (THRIVE) was balanced between treatment groups**
  - **TDF/FTC 60%; AZT/3TC 30%; ABC/3TC 10%**

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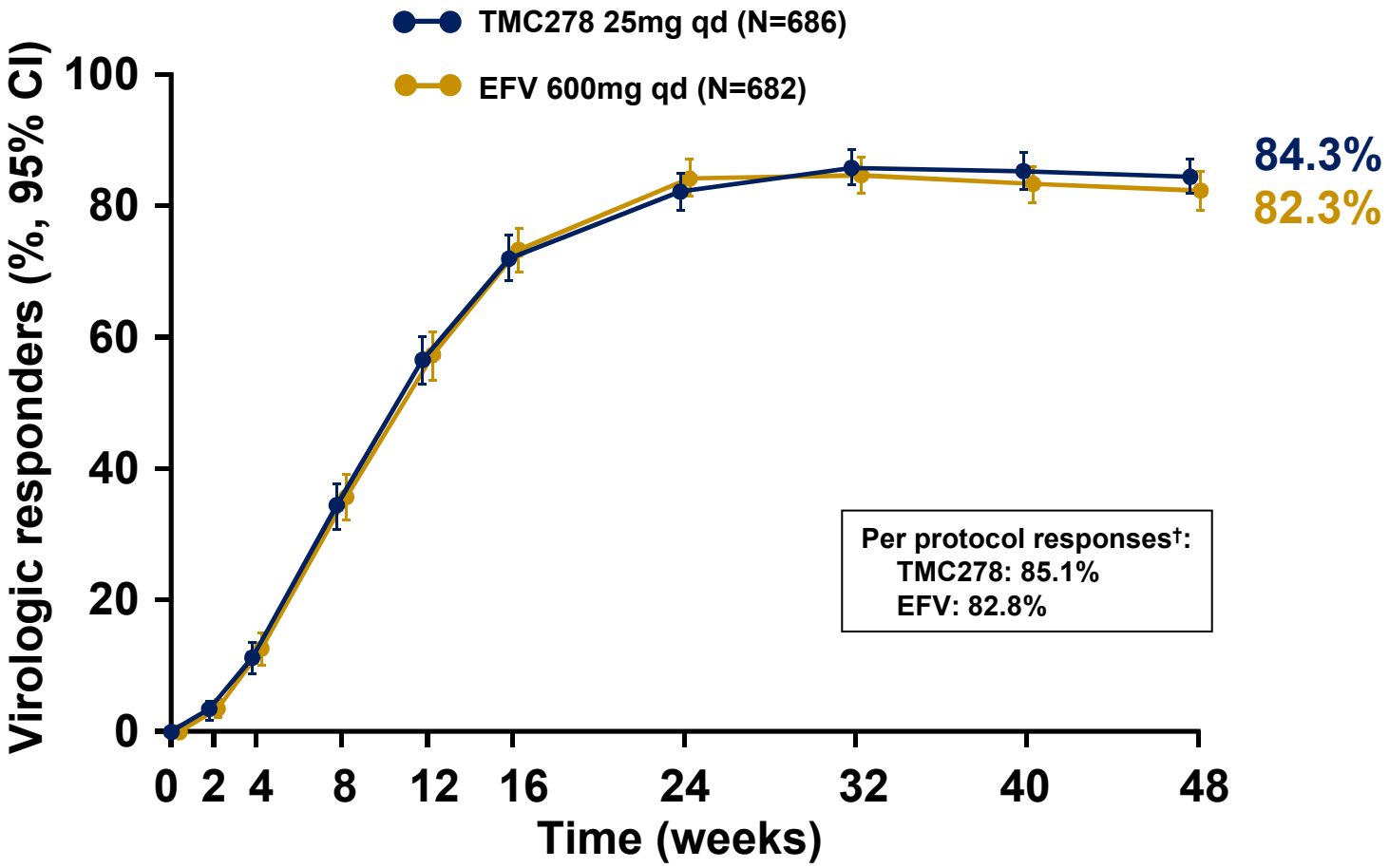
Pooled ECHO and THRIVE: VL <50 copies/mL over 48 weeks (ITT-TLOVR)



- **Mean change in CD4 cell count from baseline at Week 48 (NC=F‡): TMC278: +192 vs. EFV: +176 cells/mm^3**

CI = confidence interval; †Excluding major protocol violators; ‡missing values after discontinuation imputed with change = 0; LOCF otherwise

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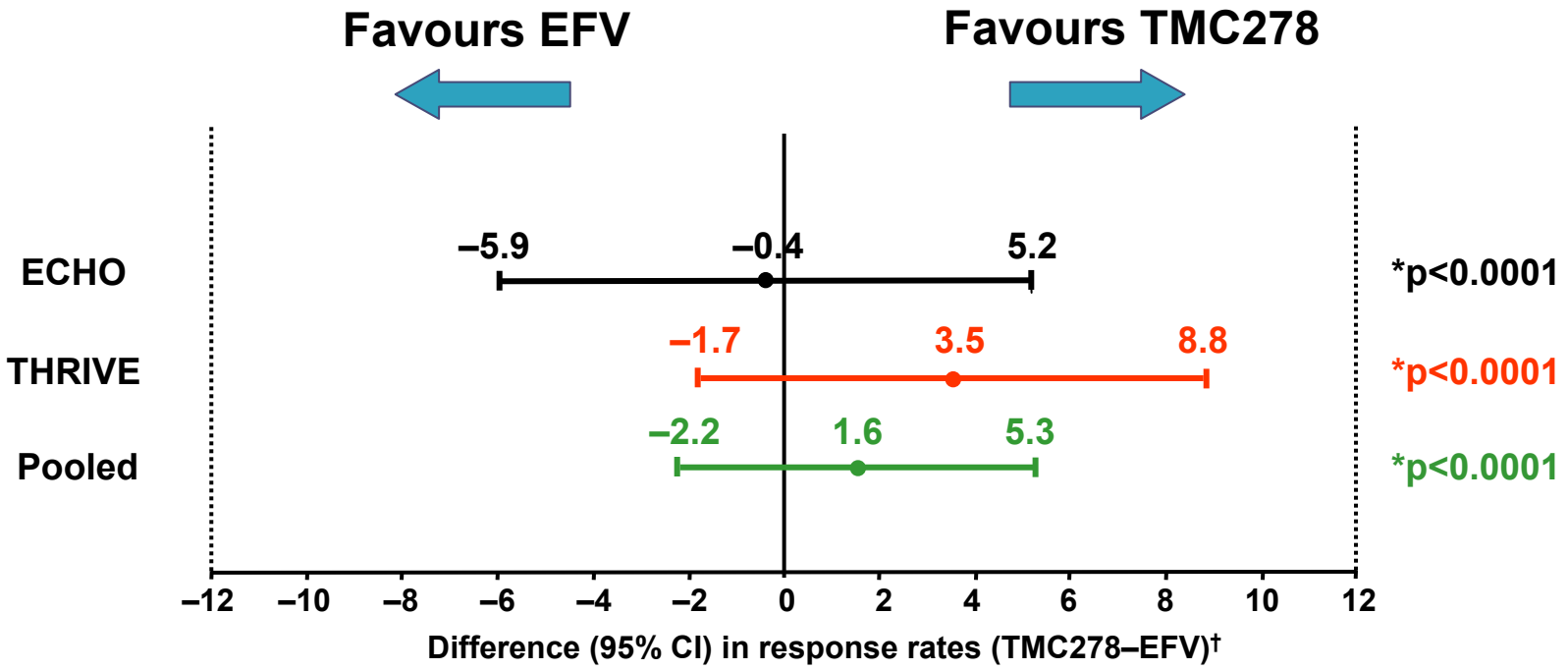
ECHO and THRIVE: difference in response rates VL <50 copies/mL (ITT-TLOVR)



*p-value for non-inferiority at 12% margin; †Estimated by logistic regression adjusted for stratification factors

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ECHO and THRIVE: ITT-TLOVR outcome at Week 48

Outcome at Week 48†, %	Pooled		ECHO		THRIVE	
	TMC278 N=686	EFV N=682	TMC278 N=346	EFV N=344	TMC278 N=340	EFV N=338
VL <50 copies/mL	**84.3**	**82.3**	**82.9**	**82.8**	**85.6**	**81.7**
Virologic failure‡	**9.0**	**4.8**	**11.0**	**4.4**	**7.1**	**5.3**
– Rebounder	3.5	2.2	4.6	2.3	2.4	2.1
– Never suppressed	5.5	2.6	6.4	2.0	4.7	3.3
Discontinued due to AE	**2.0**	**6.7**	**1.7**	**7.3**	**2.4**	**6.2**
Discontinued for other reasons§	**4.5**	**5.7**	**4.3**	**5.5**	**4.7**	**5.9**
Death	**0.1**	**0.4**	**0**	**0**	**0.3**	**0.9**

†Analysis performed up to Week 48; ‡Determined by TLOVR in the ITT population: confirmed response before Week 48 and confirmed rebound (rebounders) at or before Week 48, or no confirmed response before Week 48 (never suppressed); §Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, sponsor's decision; AE = adverse event

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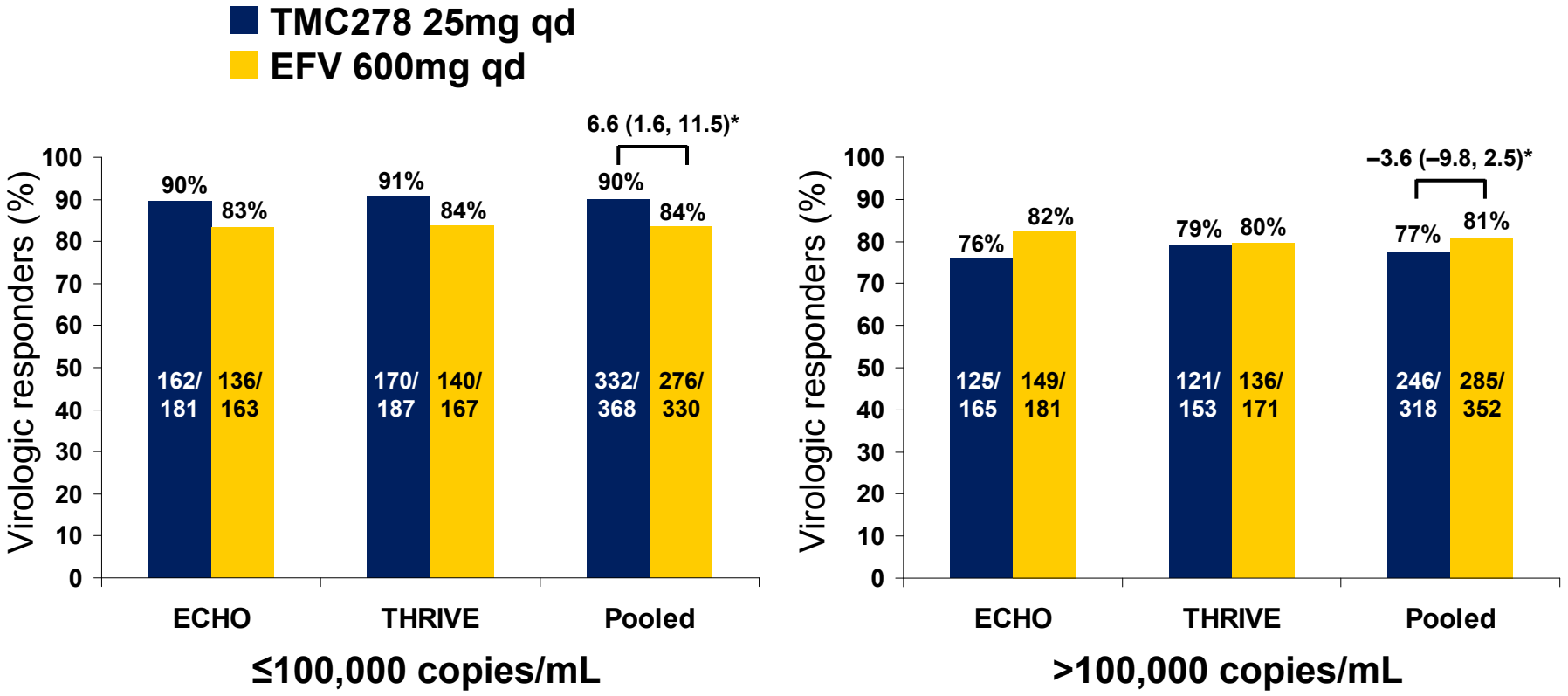
ECHO and THRIVE: VL <50 copies/mL by baseline VL (ITT-TLOVR)



- NRTI background had no effect on virologic response
- No differences between treatment groups in virologic response by gender, region or race

*Difference in response rates (95% CI)

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Pooled ECHO and THRIVE: summary of resistance findings

	TMC278 N=686	EFV N=682
Virologic failure with resistance data, n	**62**	**28**
No NNRTI[1] or NRTI[2] RAMs	**29%**	**43%**
Emergent† NNRTI[1] RAMs	**63%**	**54%**
– Most frequent NNRTI RAM	**E138K**	**K103N**
Emergent† NRTI[2] RAMs	**68%**	**32%**
– Most frequent NRTI RAM	**M184I**	**M184V**

- **31/62 (50%) of TMC278 failures were phenotypically resistant to TMC278**
  - **Of these, 90% were phenotypically cross-resistant to etravirine**

Virologic failure determined in the ITT population with all available data, regardless of time of failure and reason for discontinuation, n: TMC278 = 72 and EFV = 39
†At least one emergent NNRTI[1] or NRTI[2] RAM

[1]Tambuyzer L et al. Antivir Ther 2009;14:103–9
[2]Johnson VA et al. Top HIV Med 2009;17:138–45
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Pooled ECHO and THRIVE: adverse event summary†

	TMC278 N=686	EFV N=682	p-value TMC278 vs. EFV
Median treatment duration, weeks	56	56	
Any serious AE, %	7	8	NS
Any AE,%	90	92	NS
Grade 2–4 AE at least possibly related to treatment, %	16	31	<0.0001
Discontinuations due to AEs, %	3	8	0.0005
Most common AEs of interest,§ %			
Any neurological AE	17	38	<0.0001‡
Dizziness	8	26	<0.0001‡
Any psychiatric AE	15	23	0.0002‡
Abnormal dreams/nightmares	8	13	0.0061‡
Rash (any type)	3	14	<0.0001‡

NS = non significant; †Safety analyses performed using all available data, including beyond Week 48; ‡Fisher's Exact test, predefined analysis for these AEs; §Well-described AEs associated with current NNRTIs at least possibly related to treatment and observed in ≥10% of patients in either group (all grades)

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Pooled ECHO and THRIVE: grade 3 or 4 laboratory abnormalities

Incidence, %	TMC278 N'=685	EFV N'=670	p-value TMC278 vs. EFV
Any grade 3 or 4 laboratory abnormality	10.9	17.6	≤0.001
Increased:			
Alanine aminotransferase (ALT)	1.5	3.4	<0.05
LDL cholesterol†	0.7	4.1	<0.0001
Triglycerides†	0.3	2.2	≤0.001
Total cholesterol†	0.1	2.5	<0.0001

Worst grade, treatment-emergent events occurring in ≥2% of patients in either group and showing statistically significant differences between treatment groups by Fisher's Exact test, post-hoc analyses; N' = number with available test results; †Lipid samples taken fasting

- **Minimal change in mean serum creatinine in both groups (TMC278 <0.1 and EFV 0 mg/dL)**
  - change in TMC278 group likely related to changes in tubular secretion of creatinine (based on cystatin C results)
  - no grade 3 or 4 creatinine increases with TMC278
  - no discontinuations due to renal AEs or cases of acute renal failure
- **No difference in change in QTc interval between TMC278 and EFV groups**

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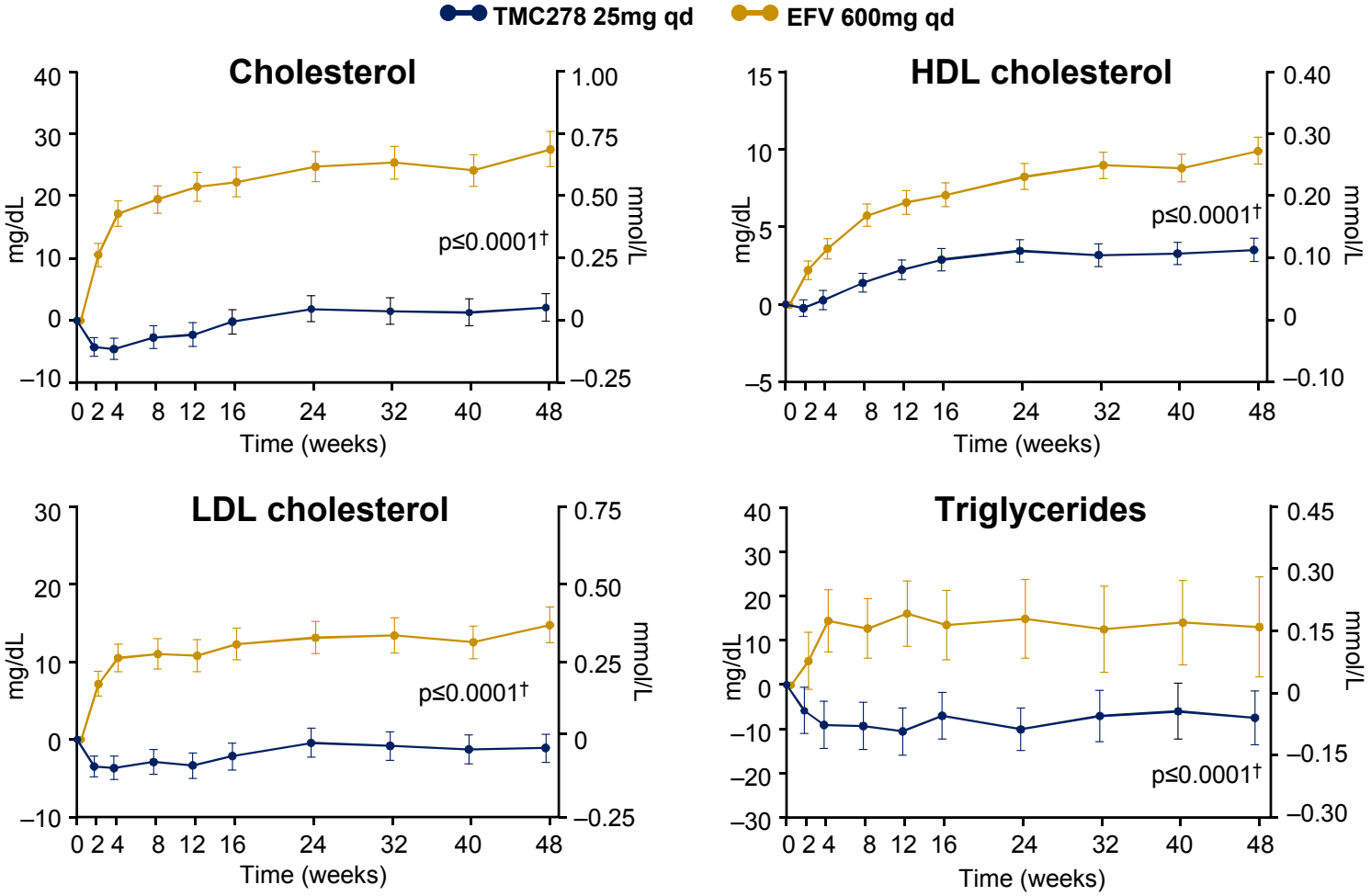
Pooled ECHO and THRIVE: mean (±95% CI) change from baseline in lipids



- **No difference between groups in total cholesterol/HDL-C ratio at Week 48**

†p value vs. EFV at Week 48 (non-parametric Wilcoxon rank-sum test)

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Phase III Conclusions at Week 48

- **TMC278 25mg once daily demonstrated a high response rate**
  - **TMC278 84.3% vs. EFV 82.3% <50 copies/mL**
  - **TMC278 was non-inferior to EFV in each trial**
- **Rate of virologic failure: TMC278 9.0% vs. EFV 4.8%**
  - **Difference in VF rates smaller in THRIVE than in ECHO**
- **TMC278 had significant tolerability advantages over EFV:**
  - **Lower rate of discontinuations due to AEs**
  - **Half the incidence of grade 2–4 AEs† (16% vs. 31%)**
  - **Lower rates of dizziness, abnormal dreams/nightmares and rash**
  - **Fewer grade 3/4 lipid abnormalities**
- **TMC278 was efficacious and well tolerated in a large and diverse group of treatment-naïve patients**

A single tablet regimen with TDF/FTC is under development[1]

†At least possibly related to treatment

[1]Mathias A et al. XVIIIth IAC 2010; Abstract LBPE17

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