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Pooled week 48 safety and efficacy results from the ECHO and THRIVE phase III trials comparing TMC278 vs EFV in treatment-naïve, HIV-1-infected patients

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Introduction

Pooled 48-week primary analysis results of two double-blind, randomised, TMC278 Phase III trials, ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725), are presented.

Methods

Treatment-naïve adult patients (N=1368) received (1:1) TMC278 25mg qd or EFV 600mg qd, plus TDF/FTC (ECHO), or TDF/FTC, AZT/3TC or ABC/3TC (THRIVE). The primary objective was to demonstrate non-inferiority (12% margin) of TMC278 to EFV in confirmed virologic response (viral load [VL] <50 copies/mL ITT-TLOVR algorithm) at Week 48.

Results

Overall virologic response rates at Week 48 were high (Figure 1).TMC278 showed non-inferior efficacy versus EFV. The impact of adherence, in addition to other factors, such as baseline viral load and exposure, on virologic response will be presented. Incidences of the following tolerability measures were significantly lower in the TMC278 group than in the EFV group: adverse events (AEs) leading to discontinuation (3% vs. 8%, respectively; p=0.0005), grade 2-4 AEs at least possibly related to treatment (16% vs. 31%; p<0.0001), rash (3% vs 14%; p<0.0001), dizziness (8% vs. 26%; p<0.0001), abnormal dreams/nightmare (8% vs. 13%; p=0.0061), and grade 3/4 laboratory abnormalities for lipids (p≤0.001).

Conclusions

At Week 48, TMC278 demonstrated a high virologic response rate (≥83%) and non-inferior efficacy versus EFV when administered with NRTIs in both Phase III trials. The virologic failure rate was significantly higher with TMC278, while the incidences of AEs leading to discontinuation were significantly lower with TMC278. Grade 2-4 AEs at least possibly related to treatment were half as frequent with TMC278 compared with EFV. In addition, incidences of dizziness, abnormal dreams/nightmare and rash were significantly lower for TMC278, and TMC278 had significantly fewer grade 3/4 lipid abnormalities than EFV.

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	TMC278 25mg qd (n=686)	Efavirenz 600mg qd (n=682)	Difference between groups
Efficacy (Week 48 outcomes)			
VL <50 copies/mL (ITT-TLOVR), % [95% CI]*	84	82	2.0 [-2.0,6.0]
ECHO, n (%) [95% CI]	287/346 (83)	285/344 (83)	0.1 [-5.5,5.7]
THRIVE, n (%) [95% CI]	291/340 (86)	276/338 (82)	3.9 [-1.7,9.5]
VL <50 copies/mL (per-protocol, ITT-TLOVR), n (%) [95% CI]	569/669 (85)	548/662 (83)	2.3 [-1.7,6.2]
Virologic failures,† %	9	5	ND
Discontinued due to AE/death, %	2	7	ND
Discontinued for other reasons, %	5	6	ND
Mean [95% CI] increase from baseline in CD4 count (NC=F‡), cells/mm^3	192 [181,203]	176 [165,188]	NS
Resistance**			
Virologic failure,§ n	72	39	p=0.0014
Failures with resistance data, n	62	28	ND
Failures developing phenotypic resistance to their treatment NNRTI, n	31/62	12/28	ND
Failures developing NNRTI mutations, n	39/62	15/28	ND
Failures developing IAS-USA NRTI mutations, n	42/62	9/28	ND
Most frequent NNRTI and NRTI mutations	E138K, M184I	K103N, M184V	NA
Safety,¶**			
Grade 2–4 AE at least possibly related to treatment, %	16	31	p<0.0001#
Serious AEs, %	7	8	NS
AEs leading to discontinuation, %	3	8	p=0.0005
AEs of interest at least possibly related to treatment¥, %			
Psychiatric	15	23	p=0.0002#
Abnormal dreams/nightmare	8	13	p=0.0061#
Neurological events of interest	17	38	p<0.0001#
Dizziness	8	26	p<0.0001#
Rash (any type)	3	14	p<0.0001#

ITT-TLOVR = intent-to-treat-time-to-loss of virologic response; CI = confidence interval; ND = not determined because not predefined; NS = non-significant; NA = not applicable. *Based on normal approximation; **p-value for Fisher's Exact test; †Rebound or never suppressed; ‡NC=F = non completer = failure: missing values after discontinuation imputed with change = 0; Last observation carried forward otherwise; §Virologic failure determined in the ITT population with all available data, regardless of time of failure and reason for discontinuation; ¶Safety analyses performed using all available data, including beyond Week 48; #Predefined analysis for these AEs; ¥Observed in ≥10% of patients in the TMC278 group or EFV group and excluding laboratory abnormalities reported as an AE

Figure 1

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