Pooled Week 96 efficacy, resistance and safety results from the double-blind, randomised, Phase III trials comparing rilpivirine (RPV, TMC278) versus efavirenz (EFV) in treatment-naïve, HIV-1-infected adults

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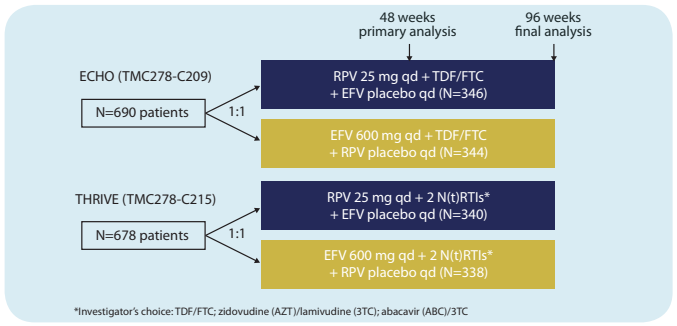
Introduction

- ECHO (TMC278-C209, NCT00540449)[1] and THRIVE (TMC278-C215, NCT00543725)[2] were global, randomised, double-blind, double-dummy, Phase III trials in treatment-naïve, HIV-1-infected adults (Figure 1)
  - In the Week 48 primary analysis, RPV 25 mg qd showed noninferior efficacy to EFV 600 mg qd (primary objective), in each trial
  - RPV had significantly lower rates of grade 2–4 adverse events (AEs) at least possibly related to treatment, rash, dizziness, abnormal dreams/nightmares, and significantly lower lipid elevations than EFV.[1,2]
- In a preplanned pooled Week 48 primary analysis of these two trials
  - 84% of patients in the RPV group and 82% of patients in the EFV group achieved viral load <50 copies/mL (difference in response: 2.0% [95% confidence interval (CI): −2.0%, 6.0%]; intent-to-treat, time-to-loss-of-virologic-response [ITT-TLOVR] algorithm)
  - Responses in the baseline viral load ≤100K copies/mL subgroup were 90% (RPV; N′=368) and 84% (EFV; N′=330) (difference: 6.6% [1.6%, 11.5%]) and in the baseline viral load >100K copies/mL subgroup were 77% (RPV; N′=318) vs 81% (N′=352; EFV) (difference: −3.6% [−9.8%, 2.5%].[3]
- RPV is approved in the USA as a single-agent tablet[4] and is being developed as a fixed-dose single-tablet regimen with tenofovir (TDF)/emtricitabine (FTC).[5]
- Here we present the pooled 96-week efficacy, safety and virology results.

Methods

Figure 1. Design of the RPV Phase III studies.



*Investigator's choice: TDF/FTC; zidovudine (AZT)/lamivudine (3TC); abacavir (ABC)/3TC

- Main inclusion criteria were viral load ≥5,000 copies/mL, no NNRTI resistance-associated mutations (RAMs) (from 39 NNRTI RAMs based on a list of 44[6]) and sensitivity to the N(t)RTIs (determined using Virco®TYPE).
- Stratification factors were screening viral load (ECHO and THRIVE) and N(t)RTI background (THRIVE only).
- Patients were recommended to take RPV/RPV placebo with food and EFV/EFV placebo on an empty stomach, at bedtime.
- The primary objective was to demonstrate noninferiority (12% margin) versus EFV in confirmed response (viral load <50 copies/mL, ITT-TLOVR algorithm) at Week 48.
- Secondary objectives included efficacy and safety/tolerability over 96 weeks.

Results

Demographics and baseline characteristics

- Overall (N=1,368), baseline patient demographics and disease characteristics were similar between treatment groups within each trial (Table 1). Background regimens (THRIVE) were balanced between treatment groups: TDF/FTC 60%; AZT/3TC 30%; ABC/3TC 10%.

Table 1. Demographics and baseline characteristics.

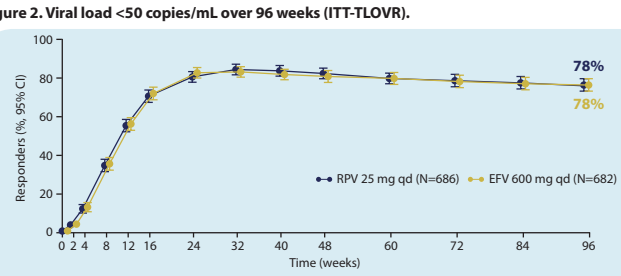
Baseline parameter	RPV N=686	EFV N=682
Female, %	25	24
Median age, years	36	36
Race, %		
Caucasian	61	60
Black	24	23
Asian	11	14
Other races/not stated	3	3
Median log_{10} viral load, copies/mL (min–max)	5 (2–7)	5 (3–7)
Baseline viral load copies/mL, % >100K*	46	52
Median CD4 cell count, cells/mm³ (min–max)	249 (1–888)	260 (1–1,137)
Hepatitis B or C co-infection, %	7	9

*Median baseline viral load, copies/mL (interquartile range [IQR]) in patients with baseline viral load >100K copies/mL was RPV 235K (152–443K) vs EFV 236K (150–460K), and in patients with baseline viral load ≤100K copies/mL it was RPV 37K (18–59K) vs EFV 34K (16–62K)

Efficacy

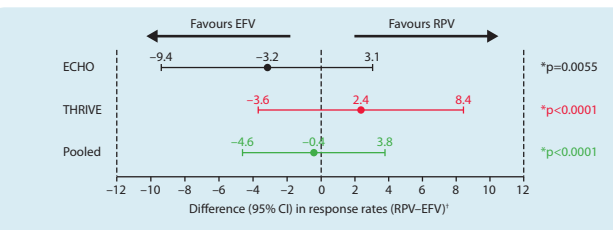
- Similar response rates for RPV and EFV were seen at Week 96 (Figures 2 and 3 and Table 2).

Figure 2. Viral load <50 copies/mL over 96 weeks (ITT-TLOVR).



- Mean change in CD4 cell count from baseline at Week 96 (missing values after discontinuation imputed with change = 0; last observation carried forward otherwise): RPV: +228 (N=685) vs EFV: + 219 cells/mm³ (N=682).

Figure 3. Difference in response rates at Week 96: viral load <50 copies/mL (ITT-TLOVR).



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

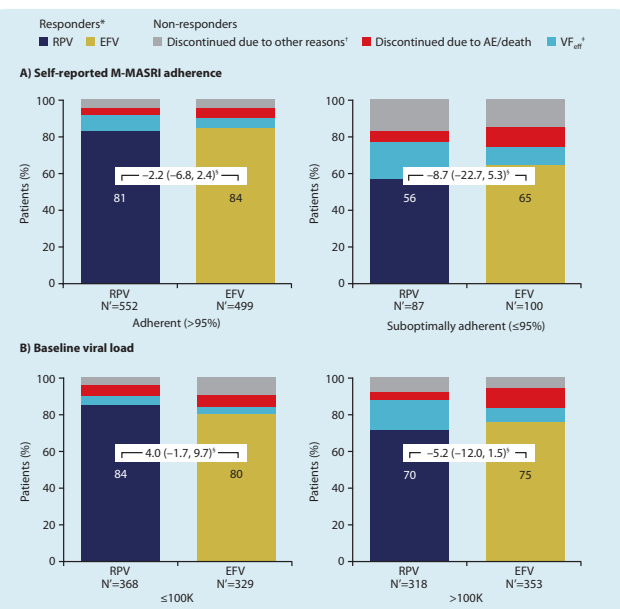
Table 2. ITT-TLOVR outcome at Week 96.

Outcome at Week 96,† n (%)	RPV N=686	EFV N=682
Viral load <50 copies/mL	532 (78)	529 (78)
VF_{eff}‡	79 (12)	40 (6)
Rebounder	44 (6)	27 (4)
Never suppressed	35 (5)	13 (2)
Discontinued due to AE	26 (4)	52 (8)
Discontinued for other reasons§	48 (7)	55 (8)
Death	1 (0.1)	6 (1)

†Analysis performed up to Week 96; ‡VF_{eff} = virologic failure determined by TLOVR in the ITT population: confirmed response before Week 96 and confirmed rebound (rebounders) at or before Week 96, or no confirmed response before Week 96 (never suppressed); §Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, sponsor's decision

- Similar response rates for RPV and EFV were seen at Week 96, based on the ITT snapshot analysis (last viral load value in the Week 96 window [90–103 weeks] <50 copies/mL; missing = failure): RPV 76% vs EFV 77%; difference between groups −0.15% (95% CI: −4.7%, 4.3%) and in the per protocol TLOVR analysis: RPV 79% vs EFV 78%; difference 0.4% (−4.0%, 4.9%).
- The majority of patients reported >95% adherence. Response rates were high and similar between treatment groups in patients with >95% reported adherence or baseline viral load ≤100K (Figure 4). Suboptimal adherence (≤95%) and baseline viral load >100K were associated with lower responses in both groups.

Figure 4. ITT-TLOVR outcome at Week 96: A) self-reported Modified Medication Adherence Self-Report Inventory (M-MASRI) adherence. B) baseline viral load.



*Responders = patients with viral load <50 copies/mL, ITT-TLOVR algorithm; †Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, sponsor's decision; ‡VF_{eff} determined by TLOVR in the ITT population: confirmed response before Week 96 and confirmed rebound (rebounders) at or before Week 96, or no response before Week 96 (never suppressed); §Difference (95% CI) in response rates (RPV-EFV)

- Overall responses declined with lower CD4 cell counts in both treatment groups. Responses were (≥200 cells/mm³): RPV 82% vs EFV 79%, (≥50–<200 cells/mm³): RPV 71% vs EFV 75% and (<50 cells/mm³): RPV 56% vs EFV 69%.

Resistance

- A similar proportion of virologic failures as determined in the resistance analysis (VF_{res}) were observed for both groups between Week 48 and 96 (Table 3).

Table 3. VF in the resistance analysis (VF_{res}).*

VF_{res}, n (%)	RPV N=686	EFV N=682
VF_{res} (all)	**96 (14)**	**52 (8)**
Rebounder	52 (8)	34 (5)
Never suppressed	44 (6)	18 (3)
VF_{res} (up to Week 48)	**73 (11)**	**36 (5)**
Rebounder	29 (4)	18 (3)
Never suppressed	44 (6)	18 (3)
VF_{res} (after Week 48 and up to Week 96†)	**22 (3)**	**16 (2)**
Rebounder	21 (3)	15 (2)
Never suppressed	1 (0.1)	1 (0.1)

*VF_{res} included all ITT patients with virologic failure regardless of time of failure and/or discontinuation reason provided the following criteria were met: first achieved two consecutive viral load values <50 copies/mL followed by two consecutive (or single, when last available) viral load values ≥50 copies/mL or stopped treatment while not suppressed (rebounder), or never achieved two consecutive viral load values <50 copies/mL and had an increase in viral load ≥0.5 log_{10} copies/mL above the nadir (never suppressed); †One VF_{res} occurred after Week 96 in the RPV group

- From Week 48 to 96, the proportion of VF_{res} who developed NNRTI RAMs was similar between groups (RPV: 6/18 [33%] vs EFV: 4/14 [29%]), however, there were more VF_{res} who developed N(t)RTI RAMs for RPV (6/18 [33%]) than for EFV (2/14 [14%]) (Table 4).

Table 4. Summary of resistance findings.

Time of failure	RPV N=686 All*	RPV N=686 Up to Week 48	RPV N=686 Week 48 to 96*	EFV N=682 All	EFV N=682 Up to Week 48	EFV N=682 Week 48 to 96
VF_{res} with resistance data, n	86	67	18	42	28	14
No emergent NNRTI[6] and N(t)RTI RAMs,[7] n (%)	35 (41)	24 (36)	11 (61)	19 (45)	11 (39)	8 (57)
Any emergent‡ NNRTI[6] and/or N(t)RTI RAMs,[7] n (%)	51 (59)	43 (64)	7 (39)	23 (55)	17 (61)	6 (43)
Any emergent‡ NNRTI RAMs,[6] n (%)	46 (53)	39 (58)	6 (33)	20 (48)	16 (57)	4 (29)
Most frequent NNRTI RAM, n (%)	E138K 31 (36)	E138K 27 (40)	E138K 3 (17)	K103N 14 (33)	K103N 11 (39)	K103N 3 (21)
Any emergent‡ N(t)RTI RAMs,[7] n (%)	48 (56)	41 (61)	6(33)	11 (26)	9 (32)	2 (14)
Most frequent N(t)RTI RAM, n (%)	M184I 32 (37)	M184I 27 (40)	M184I 4 (22)	M184V 6 (14)	M184V 6 (21)	M184I 2 (14)

*One VF_{res} occurred after Week 96 in the RPV group (E138K, K219E, M184I); †At least one emergent NNRTI RAM (from the NNRTI RAM list) or IAS-USA N(t)RTI[7] RAM

Safety

- RPV showed lower incidences than EFV of grade 2–4 overall AEs at least possibly related to treatment, AEs leading to discontinuation, rash, dizziness, abnormal dreams/nightmares (Table 5) and grade 2–4 lipid abnormalities (Table 6).
- The 96-week analysis revealed that there were no new safety concerns beyond Week 48 in both treatment groups, and only 2% of RPV and 4% of EFV patients reported at least possibly treatment-related grade 2–4 AEs during the second year of treatment (Table 5).

Table 5. AE summary.*

Median treatment duration, weeks	RPV N=686	RPV N=686 104		EFV N=682	EFV N=682 104		All p value RPV vs EFV
Incidence, n (%)	All*	Up to Week 48†	Week 48 to 96†	All*	Up to Week 48†	Week 48 to 96†	
Any serious AE	65 (9)	45 (7)	20 (3)	71 (10)	52 (8)	19 (3)	
Grade 2–4 AE at least possibly related to treatment	116 (17)	99 (14)	14 (2)	226 (33)	206 (30)	26 (4)	<0.0001§
Discontinuations due to AEs‡	28 (4)	21 (3)	5 (1)	58 (9)	47 (7)	7 (1)	
Most common AEs of interest¶							
Any neurological AE	119 (17)	111 (16)	3 (<1)	259 (38)	255 (37)	2 (<1)	<0.0001§
Dizziness	55 (8)	54 (8)	1 (<1)	182 (27)	182 (27)	1 (<1)	<0.0001§
Any psychiatric AE	107 (16)	95 (14)	5 (1)	166 (24)	149 (22)	9 (1)	<0.0001§
Abnormal dreams/nightmares	57 (8)	53 (8)	1 (<1)	90 (13)	86 (13)	2 (<1)	0.0039§
Rash (any type)	29 (4)	27 (4)	3 (<1)	103 (15)	102 (15)	0	<0.0001§

*Analysis performed using all available data, including beyond Week 96; †Patients were counted more than once in the Week 0–48 and Week 48–96 periods, and data after Week 96 are not included in the Week 48–96 period; ‡The most common AEs leading to discontinuation were any rash and depression; §Fisher's Exact test, preplanned 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)

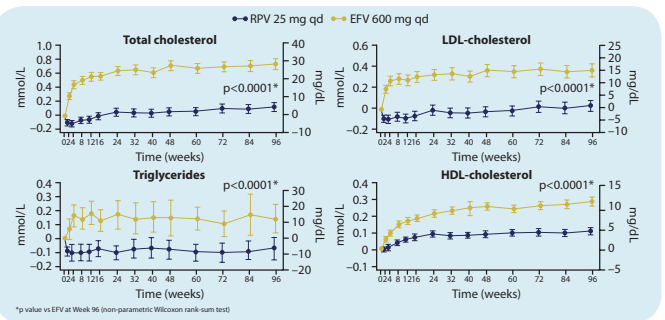
Table 6. Grade 2–4 laboratory abnormalities.*

Incidence, n (%)	RPV N=686 All†	RPV N=686 Up to Week 48‡	RPV N=686 Week 48 to 96‡	EFV N=682 All†	EFV N=682 Up to Week 48‡	EFV N=682 Week 48 to 96‡
Any grade 2–4 laboratory abnormality	317 (46)	251 (37)	161 (23)	395 (58)	334 (49)	222 (33)
Hypophosphataemia	83 (12)	57 (8)	39 (6)	90 (13)	63 (9)	37 (5)
Pancreatic amylase	54 (8)	38 (6)	24 (3)	64 (9)	56 (8)	17 (2)
Hyperglycaemia (fasted)	50 (7)	32 (5)	24 (3)	45 (7)	29 (4)	24 (4)
LDL-C (fasted)	47 (7)	34 (5)	28 (4)	121 (18)	87 (13)	70 (10)
Total cholesterol (fasted)	49 (7)	32 (5)	31 (5)	149 (22)	112 (16)	95 (14)
AST	44 (6)	30 (4)	17 (2)	69 (10)	56 (8)	17 (2)
ALT	43 (6)	33 (5)	17 (2)	75 (11)	65 (10)	21 (3)

*Treatment-emergent events occurring in ≥5% of patients in either group; †Analysis performed using all available data, including beyond Week 96; ‡Patients were counted more than once in the Week 0–48 and Week 48–96 periods, and data after Week 96 are not included in the Week 48–96 period; LDL-C = low-density lipoprotein-cholesterol; AST = aspartate aminotransferase; ALT = alanine aminotransferase

- Minimal changes in median (IQR) serum creatinine were seen in both groups: RPV 0.1 mg/dL (0.03 to 0.2 mg/dL) and EFV 0.01 mg/dL (−0.02 to 0.1 mg/dL); the smallest changes were seen with AZT/3TC
  - Change in the RPV group was likely related to changes in tubular secretion of creatinine (based on cystatin C results)
  - One RPV patient had a grade 3 creatinine increase and one EFV patient a grade 4 creatinine increase
  - No discontinuations due to renal AEs.
- No difference in change in QTc interval was seen between the RPV and EFV groups.
- RPV produced minimal changes in total cholesterol, LDL-C and triglyceride levels from baseline through 96 weeks of treatment (Figure 5).
- There were significantly greater increases in these lipid parameters and high density lipoprotein (HDL)-cholesterol in the EFV group than in the RPV group over 96 weeks, with no difference between groups in total cholesterol/HDL-cholesterol ratio.

Figure 5. Mean (±95% CI) change from baseline in lipids.



*p value vs EFV at Week 96 (non-parametric Wilcoxon rank-sum test)

Conclusions

- RPV showed sustained overall efficacy that was similar to EFV over 96 weeks (78% overall response in each group)
  - Suboptimal adherence was associated with reduced responses in both groups
  - Response was numerically higher in the RPV group with baseline VL ≤100K
  - The effect of suboptimal adherence and higher baseline viral load on VF_{eff} was more apparent with RPV than with EFV.
- At Week 48 the overall VF_{res} rate was higher with RPV than EFV, however, beyond Week 48 there were similar increases in VF_{res} for both groups.
- RPV showed lower incidences than EFV of
  - Grade 2–4 overall AEs at least possibly related to treatment
  - Dizziness, abnormal dreams/nightmares and rash (any grade) at least possibly related to treatment
  - Discontinuations due to AEs (mainly rash and dizziness)
  - Grade 2 to 4 lipid abnormalities.
- From Week 48 to 96, there were no new safety concerns with either NNRTI.
- RPV was efficacious and well tolerated in a large and diverse group of treatment-naïve patients.

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