

Raltegravir Demonstrates Durable Efficacy Through 96 Weeks: Results from STARTMRK, A Phase III Study of Raltegravir-based vs. Efavirenz-based Therapy in Treatment-Naïve HIV+ Patients

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Abstract

Background: In STARTMRK, an ongoing, double-blind study, raltegravir (RAL) had potent and non-inferior antiretroviral activity compared to efavirenz (EFV) & was generally well tolerated through 48 weeks; RAL also showed more rapid time to HIV(v)RNA <50 c/mL than EFV.

Methods: Patients with vRNA >5000 c/mL & no resistance to EFV, tenofovir (TDF) or emtricitabine (FTC) were randomized (1:1) to RAL (400 mg bid) or EFV (600 mg qhs), with TDF/FTC. Standard 96-week endpoints were evaluated. Exploratory analyses investigated the potential relationship between early virologic response and long-term CD4 response.

Results: Baseline characteristics were comparable. Results at Week 48 and 96 are shown:

	% pts (95% CI) with HIV RNA <50 copies/mL*		Change from Baseline CD4 Cells/mm ³ **	
	48-week	96-week	48-week	96-week
RAL (N=280, 281)	86	81	193 (174, 204)	240 (220, 259)
EFV (N=281, 282)	82	79	163 (148, 178)	225 (206, 244)
RAL - EFV†	4* (-2, 10)	2* (-4, 9)	26 (4, 47)	15 (-13, 42)

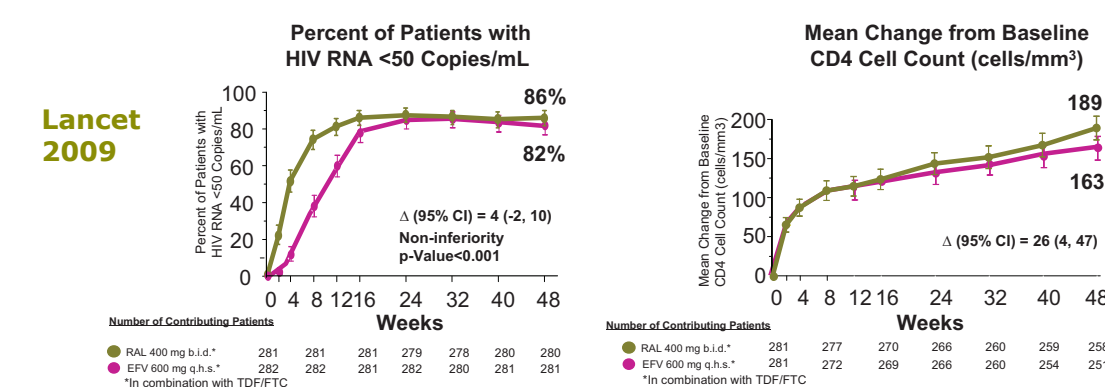
†Difference between RAL and EFV; *p-value for non-inferiority <0.001
**Non-Completer=Failure
**Baseline values carried forward for virologic failures

Conclusion: In treatment-naïve patients, RAL+TDF/FTC had durable, non-inferior antiretroviral activity sustained to 96-weeks compared to EFV+TDF/FTC & continued to be generally well tolerated.

Background

Efficacy and Safety Results through Week 48

- RAL provided potent and statistically non-inferior viral suppression compared to EFV
- RAL exerted a greater immunological effect than EFV, measured by the increase in CD4 cell counts



- RAL was generally better tolerated than EFV
 - significantly fewer overall and drug-related clinical adverse events
 - significantly lower percentages of patients with CNS side-effects

- Safety profile was similar in subjects with or without hepatitis B and/or hepatitis C

- RAL had modest effects on serum lipids

Methods

Design

- Multicenter, double-blind, randomized (1:1), active-controlled study
 - RAL 400mg BID vs EFV 600mg qhs
 - Both given with coformulated tenofovir (TDF)/emtricitabine (FTC)
- Key inclusion criteria
 - Susceptible to EFV, TDF, FTC at entry
 - No prior antiretroviral therapy
 - HIV RNA >5000 c/mL

Methods

Main Hypotheses

- RAL + TDF/FTC will have non-inferior efficacy compared to EFV + TDF/FTC
 - Primary time point: 48 weeks
 - Secondary time point: 96 weeks
- Primary analysis: NC = F
- Primary outcome: vRNA <50 c/mL
- Secondary outcomes: vRNA <400 c/mL, CD4 change from baseline
- RAL + TDF/FTC will be generally safe and well tolerated
- Outcomes: Adverse experiences (AE); CNS events; Lipid changes from baseline

Statistical Methodology

- Primary efficacy analysis: vRNA level <50 c/mL using NC = F approach for missing data
- Secondary efficacy analysis: Change in CD4 count from baseline using OF approach
- Virologic response was defined as two consecutive vRNA levels <50 c/mL measured at least a week apart

The protocol definition of virologic failure for the efficacy analyses was:

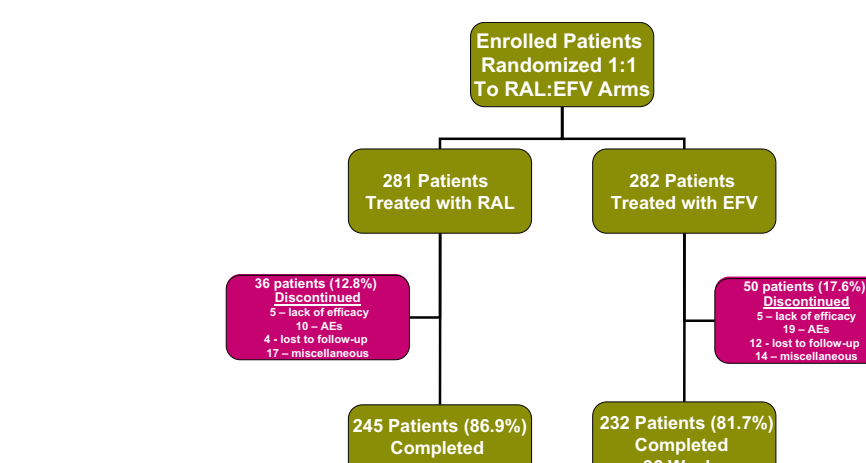
- Non-responder for those with
 - HIV RNA >50 copies/mL at the time of discontinuation for patients who prematurely discontinue study therapy or
 - HIV RNA >50 copies/mL at Week 24; or
- Virologic rebound for those with HIV RNA >50 copies/mL (on 2 consecutive measurements at least 1 week apart or discontinuation after one measurement >50 copies/mL) after initial response with HIV RNA <50 copies/mL

- Analyses of Time to Loss of Virologic Response (TLOVR) : Kaplan-Meier estimates of time to event (log rank test)

TLOVR was defined for patients who had confirmed vRNA levels <50 c/mL on two consecutive visits as the time between randomization and the first value >50 c/mL or loss to follow-up, and for patients who never achieved vRNA levels <50 c/mL on two consecutive visits as time 0

- Exploratory analysis of the relationship between an early decrease in vRNA level and subsequent increase in CD4-cell count, using OF approach
 - A linear regression model of change from baseline in CD4 cell count at Week 48/96 included the following among model predictors:
 - Baseline CD4 cell count
 - Week 8 HIV RNA log decrease
 - Treatment group

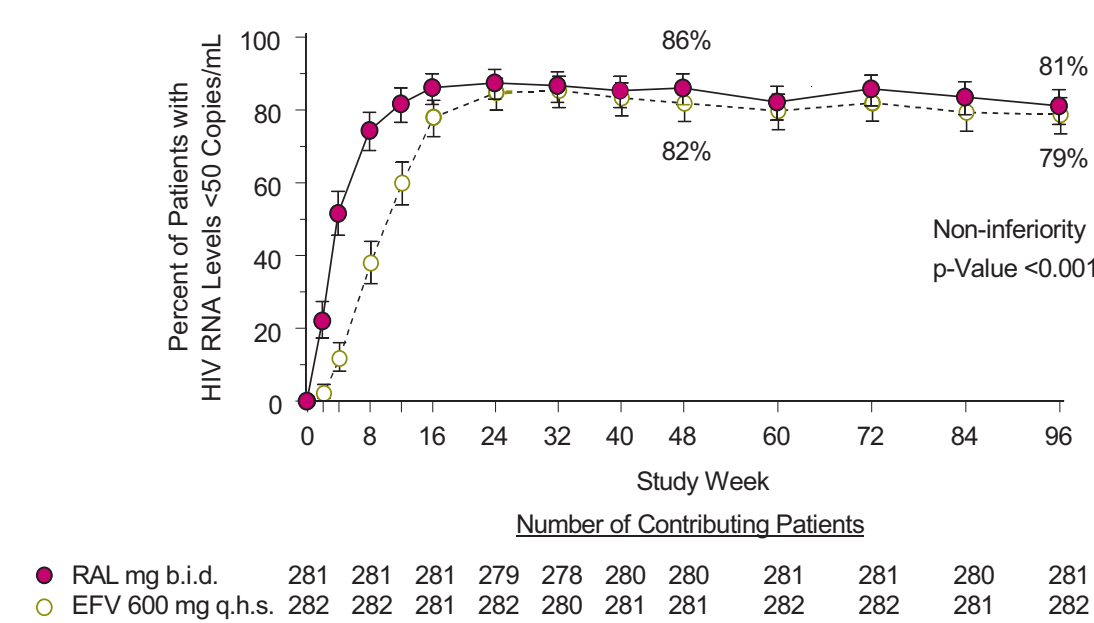
Patient Disposition at Week 96



Baseline Characteristics

	RAL Group N = 281	EFV Group N = 282
# Patients Treated	N = 281	N = 282
Age (mean, yrs)	37.6	36.9
% Male	80.8	81.9
% Non-White	58.7	56.4
vRNA copies/ml (geometric mean)	103,205	106,215
% with vRNA >10 ⁵ c/mL	54.8	50.7
Mean CD4 count (cells/μl)	218.9	217.4
% with CD4 ≤200 cells/μl	46.6	48.2
% Hepatitis B or C	6.4	5.7
% Non-Clade B	21.0	16.7

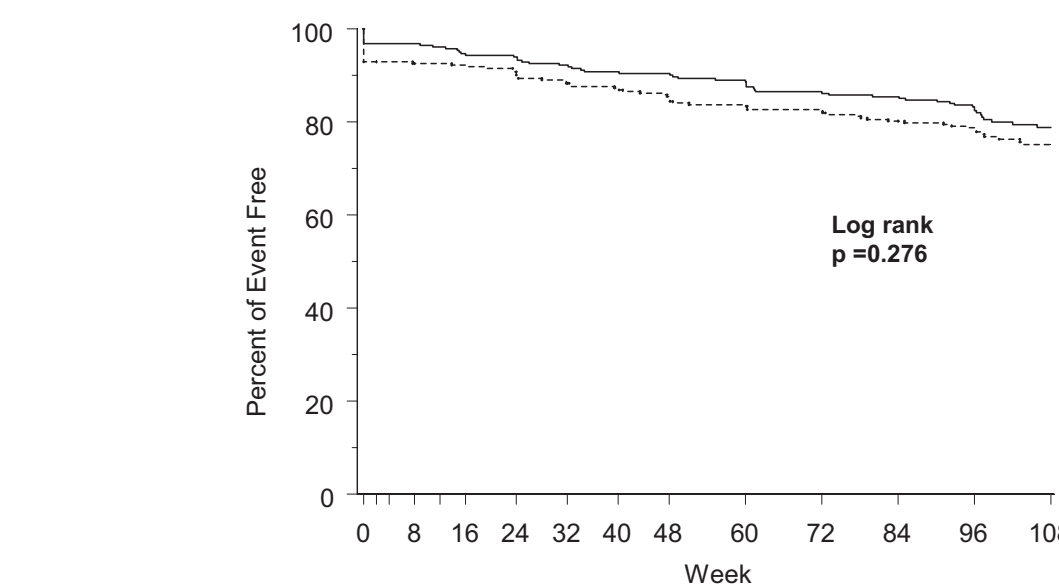
Proportion (%) of Patients (95% CI) With HIV RNA <50 c/mL Through 96 Weeks (Non-Completer = Failure)



Proportion (%) of Patients With HIV RNA <400 c/mL at 96 Weeks (Non-Completer = Failure)

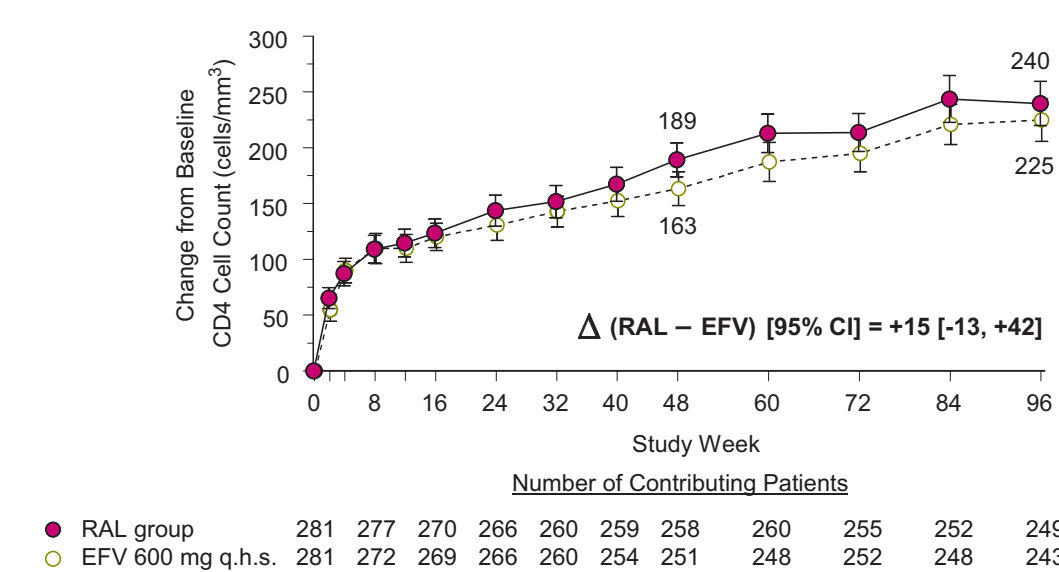
- RAL group 85% vs. EFV group 81%
- Non-inferiority p<0.001

Time to Loss of Virologic Response (HIV RNA ≥50 c/mL)



- The time to achieve virologic response was significantly shorter for patients in RAL group compared to the EFV group (log-rank test p-value of 0.001).

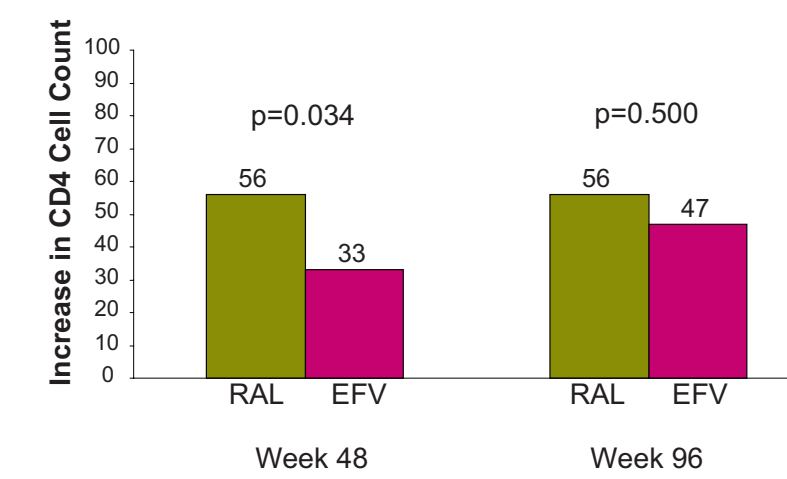
Change from Baseline in CD4 Cell Count



- RAL group
- EFV 600 mg q.h.s.

Results

Predicted Increase in CD4 Cell Counts at Week 48 and 96 Per 1 Log Drop in HIV RNA at Week 8



- At week 48, statistically significant predictors of increase in CD4 count were baseline CD4 count, log drop in week 8 vRNA level, and treatment group.

- At Week 96, statistically significant predictors of increase in CD4 count were baseline CD4 count and log drop in week 8 vRNA level.

Interval Resistance Data from Week 48 to Week 96

- Between Week 48 and 96, there were 18 new patients (12 in the RAL group and 6 in the EFV group) who met the protocol definition of virologic failure

- 7/18 patients (4 in the RAL group and 3 in the EFV group) had vRNA >400c/mL and met the resistance assay testing criteria

- 0/4 patients with evaluable data in the RAL group had detectable resistance to any of the drugs in their regimen

- 2 patients had data for both IN and RT, 1 had data for only IN, and 1 had data for only RT

- 2/3 patients with evaluable data in the EFV group had detectable resistance to any of the drugs in their regimen

- 1 had virus with no detectable resistance, 1 had virus with resistance only to EFV, and 1 had virus with resistance to EFV and FTC

Cumulative RAL Resistance Mutations by Week 96

- RAL group
 - 39 (13.9%) patients met the protocol definition of virologic failure
 - 16 patients evaluated for genotypic resistance (vRNA >400 c/mL):
 - 8 patients: RAL³ (6 were FTC³, TDF³; 2 did not amplify FTC or TDF)
 - 4 patients: RAL²* (3 were FTC², TDF²; 1 did not amplify FTC or TDF)
 - 4 patients: RAL could not be amplified (2 were FTC², TDF²; 2 were FTC², TDF²)

* RAL Mutations: 1 Q148H+G140S, 1 Q148R+G140S, 1 Y143H+L74L/M+E92Q+T97A, 1 Y143R

Cumulative EFV Resistance Mutations by Week 96

- EFV group
 - 45 (16.0%) patients met the protocol definition of virologic failure
 - 11 patients evaluated for genotypic resistance (vRNA >400 c/mL):
 - 4 patients: EFV³ (FTC³, TDF³)
 - 5 patients: EFV²* (2 were FTC², TDF²; 3 were FTC², TDF²)
 - 2 patients: EFV could not be amplified (nor FTC or TDF)

* EFV Mutations: 1 K103N, 1 K103N+V108I, 1 K103K/N+V106V/M, 1 K103N, 1 K103N+V108I+P225H

Clinical Adverse Experiences

- Overall clinical AEs:
 - RAL 266 (94.7%) vs EFV 275 (97.5%), p=0.086
- Drug-related clinical AEs:
 - RAL 132 (47.0%) vs EFV 220 (78.0%), p<0.001
- Serious clinical AEs:
 - RAL 40 (14.2%) vs EFV 34 (12.1%), p=0.457
 - Deaths: 3 (1.1%) for RAL vs 0 (0.0%) for EFV
 - causes of death were KS, metastatic lung Ca, and cerebral hemorrhage
 - none of the deaths were considered drug related
 - Malignancies: 3 (1.1%) for RAL vs 11 (3.9%) for EFV
 - 7 KS, 1 B-cell NHL, 1 anal Ca, 1 bone Ca, 1 lung Ca, 3 basal cell Ca

Cumulative CNS Adverse Events

- RAL 81 (28.8%) vs EFV 171 (60.6%) by Week 96, Δ = -31.8%, p<0.001
- CNS AEs were generally mild and transient
 - Suicidal behaviors and depression occurred at a similarly low rate in both treatment arms
- Between Weeks 48 and 96, very few additional CNS AEs were reported in either treatment group
 - The types of specific nervous system adverse experiences were similar to those observed during Weeks 0 to 48

Clinical Adverse Experiences Occurring in ≥10% of Patients in Either Treatment Group

	Raltegravir Group (N=281)		Efavirenz Group (N=282)		Raltegravir vs. Efavirenz Difference from Efavirenz	
	n	(%)	n	(%)	n	(%)
Patients with ≥1 AE	266	(94.7)	275	(97.5)	-2.86	(-6.4, 0.4)
Eye Disorders	13	(4.6)	29	(10.3)	-5.66	(-10.2, -1.4)
Gastrointestinal Disorders	140	(49.8)	155	(55.0)	-5.14	(-13.3, 3.1)
Diarrhea	50	(17.8)	72	(25.5)	-7.74	(-14.5, -0.9)
Nausea	40	(14.2)	36	(12.8)	1.47	(-4.2, 7.2)
General Disorders & Administration Site Conditions	76	(27.0)	96	(34.0)	-7.00	(-14.6, 0.6)
Fatigue	19	(6.8)	33	(11.7)	-4.94	(-9.9, -0.2)
Pruritus	34	(12.1)	29	(10.3)	1.82	(-3.5, 7.1)
Infections & Infestations	197	(70.1)	204	(72.3)	-2.23	(-9.7, 5.3)
Influenza	23	(8.2)	33	(11.7)	-3.52	(-8.6, 1.5)
Nasopharyngitis	53	(18.9)	41	(14.5)	4.32	(-1.9, 10.5)
Upper Respiratory Tract Infection	45	(16.0)	45	(16.0)	0.06	(-6.1, 6.2)
Injury, Poisoning & Procedural Complications	39	(13.9)	36	(12.8)	1.11	(-4.6, 6.8)
Metabolism & Nutrition Disorders	25	(8.9)	34	(12.1)	-3.16	(-8.4, 2.0)
Musculoskeletal & Connective Tissue Disorders	70	(24.9)	83	(29.4)	-4.52	(-11.9, 2.8)
Nervous System Disorders	106	(37.7)	169	(59.9)	-22.21	(-30.1, -14.0)
Dizziness	24	(8.5)	105	(37.2)	-28.69	(-35.2, -22.1)
Headache	65	(23.1)	71	(25.2)	-2.05	(-9.1, 5.1)
Psychiatric Disorders	81	(28.8)	105	(37.2)	-8.41	(-16.1, -0.6)
Abnormal Dreams	21	(7.5)	37	(13.1)	-5.65	(-10.9, -0.6)
Insomnia	54	(12.1)	31	(11.0)	1.11	(-4.3, 6.5)
Reproductive & Breast Disorders	17	(6.0)	29	(10.3)	-4.23	(-9.0, 0.3)
Respiratory, Thoracic & Mediastinal Disorders	83	(29.5)	71	(25.2)	4.36	(-3.0, 11.7)
Cough	36	(12.8)	26	(9.2)	3.59	(-1.6, 8.9)
Skin & Subcutaneous Disorders	81	(28.8)	118	(41.8)	-13.02	(-20.8, -5.1)
Rash	17	(6.0)	34	(12.1)	-6.01	(-10.9, -1.3)

Changes in Lipid Values at 96 Weeks

Lipid Parameter	Treatment Group	Mean Level† (SD) At Baseline	Mean Level† (SD) At Week 96	Change in Mean Level† (SD) From Baseline	P-value for Between-Group Difference
Total Cholesterol	Raltegravir	155 (36)	169 (33)	10 (29)	<0.001
	Efavirenz	156 (38)	194 (46)	38 (36)	
HDL-Cholesterol	Raltegravir	39 (13)	42 (11)	3 (8)	<0.001
	Efavirenz	38 (11)	48 (15)	10 (11)	
LDL-Cholesterol	Raltegravir	96 (32)	103 (28)	7 (25)	<0.001
	Efavirenz	93 (31)	114 (38)	21 (30)	
Total:HDL Cholesterol Ratio	Raltegravir	4 (1)	4 (1)	-0.18 (1)	0.192
	Efavirenz	4 (1)	4 (2)	-0.04 (1)	
Triglycerides	Raltegravir	125 (74)	121 (76)	-4 (75)	0.001
	Efavirenz	137 (125)	177 (245)	40 (199)	

SD, standard deviation.
†Levels are given in mg/dL.
*P-values for treatment differences were calculated from an ANCOVA model with terms for baseline lipid level and treatment. The Last-Observation-Carried-Forward approach was applied for missing data when the value was missing due to increased lipid levels (e.g., when lipid-lowering therapy had been initiated).

Conclusions

- In treatment-naïve patients given 96 weeks of therapy, RAL + TDF/FTC compared with EFV+TDF/FTC
 - had potent, durable, and statistically non-inferior efficacy
 - was associated with more rapid responses
 - was associated with similar increases in CD4 cell counts
 - was generally better tolerated
 - significantly fewer overall and drug-related clinical adverse events
 - significantly lower cumulative percentages of patients with CNS adverse experiences
 - both RAL and EFV in combination with TDF/FTC exerted only modest effects on serum lipids
- In both treatment arms, the increase in CD4 count at Week 48 and 96 was predicted by Week 8 decrease in HIV RNA level
 - Further analyses will be performed to corroborate these findings

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