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Raltegravir (RAL) Demonstrates Durable Virologic Suppression and Superior Immunologic Response with a Favorable Metabolic Profile Through 3 Years of Treatment (Tx): 156 Week (Wk) Results from STARTMRK

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Abstract

Background: As HIV tx has evolved to a paradigm of lifelong therapy, with greater relevance of co-morbidities, long-term data is essential to distinguish regimens. We report 156 Wk results from STARTMRK.

Methods: 563 Pts were randomized to RAL vs. EFV, each with TDF/FTC, in a double-blind study comparing standard efficacy endpoints and metabolic parameters. DEXA scans were obtained on a subset of Pts: 86 at baseline (BL) and Wk 48, 75 at BL and Wk 96, and 57 at BL and Wk 156. To fully characterize efficacy, 3 analytic approaches were used.

Results: Efficacy analyses at Wk 156 are summarized.

	% (n/N) of Pts with HIV RNA <50 copies/mL[1]			% (n/N) of Pts with HIV RNA <400 copies/mL[1]			Change from BL in CD4 Cell Count (cells/mm^3)
	NC=F	TRD=F	OF	NC=F	TRD=F	OF	OF[2]
RAL (N=281)	75.4 (212/281)	85.1 (212/249)	89.5 (212/237)	79.7 (224/281)	90.0 (224/249)	94.5 (224/237)	331.7
EFV (N=282)	68.1 (192/282)	77.1 (192/249)	84.6 (192/227)	72.0 (203/282)	81.5 (203/249)	89.4 (203/227)	295.2
RAL - EFV[3]	7.3* (-0.2, 14.7)	8.0* (1.2, 14.9)	4.9* (-1.3, 11.1)	7.6* (0.5, 14.6)	8.5* (2.4, 14.7)	5.2* (0.2, 10.5)	36.6 (3.9, 69.2)

[1]Difference between RAL and EFV (95%CI); *p-value for non-inferiority <0.001

[2]RAL would be considered non-inferior to EFV if the lower bound of the 95% CI for the difference in % response was above -12%, and superior to EFV if the lower bound exceeds 0.

[3]Observed Failure (OF): Pts who discontinued tx due to lack of efficacy were considered as failures thereafter.
Tx-Related Discontinuation=Failure (TRD=F): Pts who discontinued tx due to lack of efficacy or AE were considered as failures thereafter.
Non-Completer=Failure (NC=F): Pts who discontinued tx regardless of reasons were considered as failures thereafter.
[4]BL values carried forward for virologic failures.

With longer-term follow-up, RAL demonstrates greater virologic suppression and immunologic response after 3 years of tx. Drug-related clinical AEs occurred less often with RAL than EFV (49% vs. 80%; p<0.001). RAL was generally well tolerated with few discontinuations due to AEs (5% RAL, 7% EFV). At Wk 156, RAL had less impact on fasting lipids than EFV. Fat changes by DEXA appeared numerically more favorable for RAL (Total Mean % Change, +19 RAL, +31 EFV) with no patterns of fat loss after 3 years of tx.

Conclusions: After 3 years, RAL + TDF/FTC is associated with higher antiretroviral efficacy and superior CD4 responses in tx-naive Pts. The long-term tolerability as well as metabolic profile appears favorable.

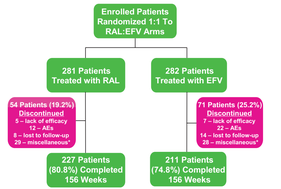
Methods

Design

- Multicenter, double-blind, randomized (1:1), active-controlled study
  - RAL 400 mg BID vs. EFV 600 mg qhs
  - Both given with co-formulated tenofovir (TDF)/emtricitabine (FTC)
- Key inclusion criteria
  - Susceptible to EFV, TDF, FTC at entry
  - No prior antiretroviral therapy
  - HIV RNA >5000 c/mL
- Main objectives
  - RAL + TDF/FTC will have non-inferior efficacy compared to EFV + TDF/FTC
    - Primary hypothesis time point: 48 weeks
    - Secondary hypothesis time point: 96 weeks
    - Long term follow-up planned through 5 years
    - 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 failure was defined as
    1) Non-responder for those with
       a) HIV RNA >50 copies/mL at the time of discontinuation for patients who prematurely discontinue study therapy *or*
       b) HIV RNA >50 copies/mL at Week 24; or
    2) 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
- Statistical Approaches to Missing Data for the Efficacy Analyses
  - To fully characterize efficacy, 3 analytic approaches were used
    - Observed failure (OF): patients who discontinued treatment due to lack of efficacy were considered as failures thereafter
    - Treatment-Related Discontinuation=Failure (TRD=F): patients who discontinued treatment due to lack of efficacy or adverse events (AE) were considered as failures thereafter
    - Non-Completer=Failure (NC=F): patients who discontinued treatment regardless of reasons were considered as failures thereafter

Results

Patient Disposition at Week 156



*Miscellaneous includes consent withdrawn, protocol deviation, and patients who completed the base protocol but who did not enter the extension as well as other.

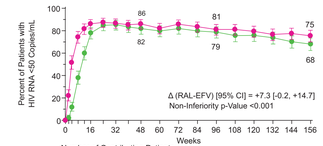
Baseline Characteristics

	All Treated Patients		Patients in the DEXA Substudy	
	Raltegravir (N = 281)	Efavirenz (N = 282)	Raltegravir (N = 55)	Efavirenz (N = 57)
Gender n (%)				
Male	227 (81)	231 (82)	51 (93)	48 (84)
Female	54 (19)	51 (18)	4 (7)	9 (16)
Race n (%)				
White	116 (41)	123 (44)	34 (62)	33 (58)
Black	33 (12)	23 (8)	14 (25)	9 (16)
Asian	36 (13)	32 (11)	0 (0)	1 (2)
Hispanic	60 (21)	67 (24)	5 (9)	11 (19)
Native American	1 (0.4)	0 (0)	0 (0)	1 (2)
Multiracial	35 (12)	36 (13)	2 (4)	2 (4)
Region n (%)				
Latin America	99 (35)	97 (34)	--	--
Southeast Asia	34 (12)	29 (10)	--	--
North America	82 (29)	90 (32)	55 (100)	57 (100)
EU/Australia	66 (23)	66 (23)	--	--
Age (years)				
18-64 n (%)	279 (99)	278 (99)	55 (100)	56 (98)
≥ 65 n (%)	2 (0.7)	4 (1.4)	0 (0)	1 (2)
Mean (SD)	37.6 (9)	36.9 (10)	37 (9)	40 (10)
Median (min, max)	37.0 (19, 67)	36.0 (19, 71)	38 (20, 61)	39 (21, 67)
CD4 Cell Count (cells/mm^3)				
N[a]	281	281	55	57
Mean (SD)	218.9 (124)	217.4 (134)	236 (157)	226 (149)
Median (min, max)	212.0 (1, 620)	204.0 (4, 807)	231 (1, 609)	202 (6, 567)
Plasma HIV RNA (log_{10} copies/mL)				
N[a]	281	282	55	57
Mean (SD)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)
Median (min, max)	5.1 (3,6)	5.0 (4,6)	4.9 (4,6)	5.0 (4,6)
Plasma HIV RNA (copies/mL)				
N[a]	281	282	55	57
Geometric Mean	103205	106215	90006	99834
Median (min, max)	114000 (400 to 750000)	104000 (4410 to 750000)	85700 (5310 to 750000)	112000 (4410 to 750000)
History of AIDS[b] n (%)				
Yes	52 (19)	59 (21)	10 (18)	8 (14)
Stratum[b] n (%)				
Screening HIV RNA ≤ 50,000	75 (27)	80 (28)	16 (29)	15 (26)
Hepatitis B or C Positive[††]	18 (6)	16 (6)	2 (4)	4 (7)
Viral Subtype n (%)				
Clade B	219 (78)	230 (82)	53 (96)	52 (91)
Non-Clade B	59 (21)	47 (17)	2 (4)	3 (5)
Missing	3 (1)	5 (2)	0 (0)	2 (4)
Baseline Plasma HIV RNA[a] n (%) copies/mL				
≤ 50,000	79 (28)	84 (30)	19 (35)	19 (33)
> 50,000	202 (72)	198 (70)	36 (65)	38 (67)
≤ 100,000	127 (45)	139 (49)	31 (56)	27 (47)
> 100,000	154 (55)	143 (51)	24 (44)	30 (53)
Baseline CD4 Cell Counts n (%) cells/mm^3				
≤ 50	27 (10)	31 (11)	8 (15)	9 (16)
>50 and ≤ 200	104 (37)	105 (37)	15 (27)	19 (33)
> 200	150 (53)	145 (51)	32 (58)	29 (51)
Missing	0 (0)	1 (0.4)	0 (0)	0 (0)

[a]Patients with missing results excluded.
[b]AIDS in patient's medical history was reported and determined by investigators. Patient's medical history with preferred terms consistent with CDC Category C AIDS defining conditions are also included as specified by FDA.
[††]Ab-stratification was corrected based on test results.
[††]Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C Virus.

Note: Raltegravir and Efavirenz were administered with TDF/FTC FDC.
N = Number of patients in each group.
n (%) = Number (percent) of patients in each sub-category.

Proportion (%) of Patients (95% CI) with HIV RNA <50 c/mL through 156 Weeks (Non-Completer = Failure)



Number of Contributing Patients

Raltegravir group	281	281	278	280	281	281	280	281	281	277	279	280	281
Efavirenz group	282	281	280	281	282	282	281	282	279	281	281	281	282

Summary of Efficacy at Wk 156

	% (n/N) of Pts with HIV RNA <50 copies/mL#			% (n/N) of Pts with HIV RNA <400 copies/mL#			Change from BL in CD4 Cell Count (cells/mm^3)
	NC=F	TRD=F	OF	NC=F	TRD=F	OF	OF†
RAL (N=281)	75.4 (212/281)	85.1 (212/249)	89.5 (212/237)	79.7 (224/281)	90.0 (224/249)	94.5 (224/237)	332
EFV (N=282)	68.1 (192/282)	77.1 (192/249)	84.6 (192/227)	72.0 (203/282)	81.5 (203/249)	89.4 (203/227)	295
RAL - EFV‡§	7.3* (-0.2, 14.7)	8.0* (1.2, 14.9)	4.9* (-1.3, 11.1)	7.6* (0.5, 14.6)	8.5* (2.4, 14.7)	5.2* (0.2, 10.5)	37 (4, 69)

‡Difference between RAL and EFV (95%CI); *p-value for non-inferiority <0.001.
§RAL would be considered non-inferior to EFV if the lower bound of the 95% CI for the difference in % response was above -12%, and superior to EFV if the lower bound exceeds 0.
†Observed Failure (OF): Pts who discontinued tx due to lack of efficacy were considered as failures thereafter.Tx-Related Discontinuation=Failure (TRD=F): Pts who discontinued tx due to lack of efficacy or AE were considered as failures thereafter. Non-Completer=Failure (NC=F): Pts who discontinued tx regardless of reasons were considered as failures thereafter.
#BL values carried forward for virologic failures.

STARTMRK – 156 Week Summary of Virologic Failures and Resistance Data

	Raltegravir	Efavirenz
Virologic failures	49/281 (17.4%)	53/282 (18.8%)
Resistance data available (VL > 400 c/mL)	19	16
RAL or NNRTI resistance Alone	1	4
RAL or NNRTI resistance and NRTI resistance	3	3
NRTI resistance alone	3	2

RALTEGRAVIR Group

4/281 (1.4%) developed proven RAL resistance

3/281 (1.1%) developed proven dual RAL/NRTI resistance

42/49 (85.7%) failed without evidence of resistance

RAL Mutations:

1 Q148H+G140S
1 Q148R+G140S
1 Y143Y/H+L74L/M+E92Q+T97T/A
1 Y143R

EFAVIRENZ Group

7/282 (2.5%) developed proven NNRTI resistance

3/282 (1.1%) developed proven dual NNRTI/NRTI resistance

44/53 (83.0%) failed without evidence of resistance

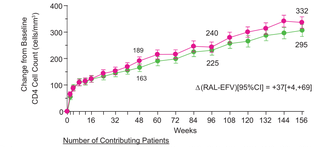
EFV Mutations:

2 K103N
1 K103N+V108I
1 K103K/N+V106V/M
1 K103K/N
1 K103N+V108I+P225H
1 K103N+G190A

Interval Resistance Data from Week 96 to Week 156

- Between Weeks 96 and 156, there were 18 new patients (10 in the RAL group and 8 in the EFV group) who met the protocol definition of virologic failure
- 1 of 3 patients with evaluable data in the RAL group had detectable resistance only to FTC
  - No new patients had detectable resistance to RAL
- 4 of 5 patients with evaluable data in the EFV group had detectable resistance to any of the drugs in their regimen: 2 had virus with resistance only to FTC, 1 had virus with resistance only to EFV, and 1 had virus with resistance to EFV, FTC and TDF

Change from Baseline in CD4 Cell Count (Observed Failure Approach)



Number of Contributing Patients

Raltegravir group	281	270	260	258	260	255	252	250	245	240	238	235	236
Efavirenz group	281	269	260	251	248	252	248	243	239	234	231	228	226

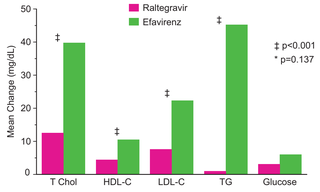
Metabolic Evaluation and DEXA Sub-Study Design

- We evaluated whether treatment was associated with metabolic abnormalities during extended follow-up through 156 weeks
  - The corresponding fasting lipid visit was at Week 144
- Treatment groups in the parent study were compared for metabolic parameters
  - Fasting lipid and glucose abnormalities according to DAIDS criteria
- DEXA scans were obtained on a subset of Patients
  - Patients at US sites were eligible
    - Only sites with access to the necessary equipment were included
  - Follow-up scans were performed at Week 48 and/or Week 96 as well as Week 156

Statistical Approaches to Missing Data for the Metabolic Analyses

- Lipid Profile
  - Last Observation Carried Forward approach
    - If patients initiated lipid-lowering therapy, last available lipid values prior to the use of lipid-lowering therapy were used in the analysis
- Body Composition (DEXA)
  - Complete data set approach
    - Patients needed to have values at both baseline and Week 48 (or Week 96 or Week 156) to be included in the analysis

Mean Change from Baseline in Metabolic Parameters at Week 144



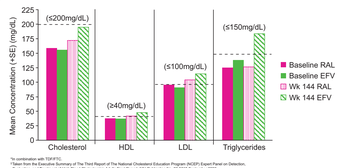
- The change from baseline in the T CHOL:HDL-C ratio was -0.20 for the RAL group and 0.04 for EFV group (p=0.061)

Number (%) of Patients with Treatment Emergent Laboratory Abnormalities by Grade (Weeks 0 - 156, Worsen Grade)

Laboratory Test	PDLC Criteria	Grade	Number (%) with PDLC	
			Raltegravir (N=281) n/m (%)	Efavirenz (N=282) n/m (%)
Blood chemistry test				
Fasting (non-random) serum LDL-C (mg/dL)	130 -159	Grade 1	46/271 (17.0)	49/262 (18.7)
	160 - 189	Grade 2	18/271 (6.6)	33/262 (12.2)
	≥190	Grade 3	4/271 (1.5)	19/262 (7.3)
Fasting (non-random) serum cholesterol (mg/dL)	200 - 239	Grade 1	60/276 (21.7)	71/267 (26.6)
	240 - 300	Grade 2	22/276 (8.0)	46/267 (17.2)
	>300	Grade 3	0/276 (0)	12/267 (4.5)
Fasting (non-random) serum triglyceride (mg/dL)	500 -750	Grade 2	3/276 (1.1)	12/267 (4.5)
	751-1200	Grade 3	1/276 (0.4)	2/267 (0.7)
	>1200	Grade 4	0/276 (0.0)	3/267 (1.1)
Fasting (non-random) serum glucose test (mg/dL)	110 - 125	Grade 1	29 /274 (10.6)	41/266 (15.4)
	126 - 250	Grade 2	11/274 (4.0)	14/266 (5.3)
	251 - 500	Grade 3	4/274 (1.5)	2/266 (0.8)
	>500	Grade 4	0/274 (0.0)	0/266 (0.0)

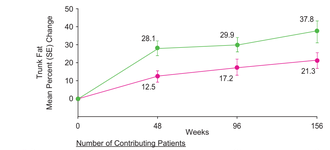
n/m=number of patients with PDLC/number of patients with that laboratory test.

Fasting Lipid Levels at Baseline and Week 144 as Compared with NCEP Goals



*In combination with TDF/FTC.
†Taken from the Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Final Report. NIH Publication No. 02-5215 September 2002.

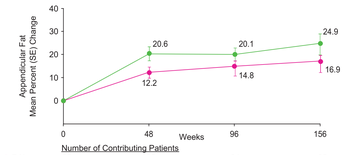
Mean Percent (%) Change (SE) in Trunk Fat Over Time (Patients with DEXA at BL and Wk 156)



Number of Contributing Patients

RAL group	25	25	24	25
EFV group	32	30	31	32

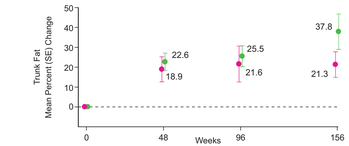
Mean Percent (%) Change (SE) in Appendicular Fat Over Time (Patients with DEXA at BL and Wk 156)



Number of Contributing Patients

RAL group	25	25	24	25
EFV group	32	30	31	32

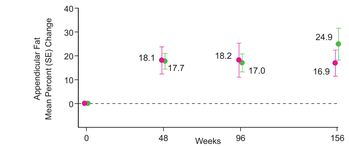
Mean Percent (%) Change (SE) in Trunk Fat Over Time (Full DEXA Subgroup)



Number of Contributing Patients

Raltegravir group	55	40	37	25
Efavirenz group	56	46	38	32

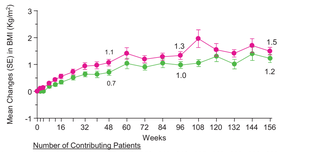
Mean Percent (%) Change (SE) in Appendicular Fat Over Time (Full DEXA Subgroup)



Number of Contributing Patients

Raltegravir group	55	40	37	25
Efavirenz group	56	46	38	32

Mean Change (SE) in BMI (kg/m^2) Over Time



Number of Contributing Patients

Raltegravir group	279	267	259	257	252	252	249	242	235	229	229	226	223
Efavirenz group	280	265	253	249	243	240	238	231	222	218	213	211	206

Lipoatrophy

- Due to attrition in Patients participating in the DEXA substudy it is difficult to interpret the data in a comparative fashion
- The majority of patients in both groups experienced modest fat gain
  - "Return to health" phenomenon
- 1/25 patients on RAL and 2/32 patients on EFV had at least 20% appendicular fat loss (lipoatrophy) at Week 156
  - There was no discordance between appendicular and trunk fat loss among these few patients
  - None of the patients with lipoatrophy identified by DEXA scanning had investigator-reported lipodystrophy as an adverse event

Clinical Adverse Experiences (AE)

- Overall clinical AEs:
  - RAL 267 (95.0%) vs. EFV 276 (97.9%), p=0.073
- Drug-related clinical AEs:
  - RAL 139 (49.5%) vs. EFV 225 (79.8%), p<0.001
- Discontinued due to clinical AE:
  - RAL 13 (4.6%) vs. EFV 21 (7.4%), p=0.215
- Serious clinical AEs:
  - RAL 46 (16.4%) vs. EFV 46 (16.3%), p=1.000
    - Deaths: 4 (1.4%) for RAL vs. 0 (0.0%) for EFV
      - Causes of death were KS, metastatic lung CA, drug toxicity and alcohol poisoning, and cerebral hemorrhage
      - None of the deaths were considered drug related
    - 32 (15 RAL vs. 17 EFV) new serious clinical AEs between Week 96 and Week 156

Conclusions

- After 3 years, RAL + TDF/FTC is associated with higher antiretroviral efficacy and superior CD4 responses in treatment-naive patients, compared to EFV + TDF/FTC
  - 75.4% vs. 68.1% <50 copies/mL (NC=F); Δ=7.3 (-0.2; 14.7); p-value for non-inferiority <0.001
  - Increase of 332 cells/mL vs. 295 cells/mL; Δ=37 (4; 69)
- The long-term tolerability as well as metabolic profile appears favorable

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STARTMRK Study Team Investigators

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All patients who participated in STARTMRK

*Denotes investigators for the DEXA substudy.

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Final size: 90"w x 42"h