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Raltegravir (RAL)-based Therapy Demonstrates Superior Virologic Suppression and Immunologic Response Compared with Efavirenz (EFV)-based Therapy, with a Favorable Metabolic Profile, Through 4 Years in Treatment-naïve Patients: 192 Week Results from STARTMRK

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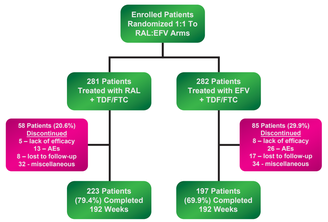
Background

- HIV treatment has evolved to lifelong therapy with greater relevance of co-morbidities
  - Long-term safety and efficacy data are essential to distinguish antiretroviral regimens
- STARTMRK is an ongoing Phase III study of RAL in treatment (tx)-naïve patients. After 3 years, RAL + tenofovir/emtricitabine (TDF/FTC) demonstrated
  - Favorable tolerability & metabolic profile
  - Non-inferior antiretroviral efficacy vs EFV + TDF/FTC
  - Superior CD4 responses vs EFV +TDF/FTC
- 4 year results from STARTMRK are presented here

Methods

- STARTMRK Study Design
  - Multicenter, double-blind, randomized (1:1), active-controlled study
    - RAL 400mg BID vs. EFV 600mg qhs
    - Both given with co-formulated TDF / 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 through 5 years; study remains double-blind; efficacy analyses beyond 96 weeks are exploratory
    - Efficacy endpoints: vRNA <50 copies/mL, CD4 change from baseline
  - RAL + TDF/FTC will be generally safe and well tolerated
    - Safety endpoints: Lipid changes from baseline, other selected laboratory abnormalities, clinical adverse events (AEs)
- Statistical Methodology
  - 3 pre-specified analytic approaches to missing data for efficacy analyses
    - Observed Failure (OF): Patients who discontinued tx due to lack of efficacy were considered as failures thereafter
    - Tx-Related Discontinuation=Failure (TRD=F): Patients who discontinued tx due to lack of efficacy or AE were considered as failures thereafter
    - Non-Completer=Failure (NC=F): Patients who discontinued tx regardless of reason were considered as failures thereafter
  - Primary efficacy analysis: vRNA level <50 c/mL using NC = F approach for missing data
    - RAL is considered non-inferior to EFV if the lower bound of the two-sided 95% CI for the difference in response proportions (RAL-EFV) remains above -12 percentage points
    - Due to the principles of closed testing, it can be further concluded that RAL is superior to EFV if the lower confidence bound exceeds zero
  - Secondary efficacy analysis: Change in CD4 count from baseline using OF approach
    - Baseline values carried forward for virologic failures
  - 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
  - Safety analyses: treatment-emergent AEs and laboratory abnormalities were tabulated; data are cumulative through Week 192

Patient Disposition at Week 192



Results

Baseline Characteristics

	All Treated Patients: Raltegravir Group (N = 281)	Efavirenz Group (N = 282)
Gender, n (%)		
Male	227 (80.8)	231 (81.9)
Female	54 (19.2)	51 (18.1)
Race, n (%)		
White	116 (41.3)	123 (43.6)
Black	33 (11.7)	23 (8.2)
Asian	36 (12.8)	32 (11.3)
Hispanic	60 (21.4)	67 (23.8)
Other	36 (12.8)	37 (13.1)
Region, n (%)		
Latin America	99 (35.2)	97 (34.4)
Southeast Asia	34 (12.1)	29 (10.3)
North America	82 (29.2)	90 (31.9)
EU/Australia	66 (23.5)	66 (23.4)
Age (years)		
Mean (SD)	37.6 (9.0)	36.9 (10.0)
Median (min, max)	37 (19 to 67)	36 (19 to 71)
Hepatitis B or C Positive†, n (%)		
Yes	18 (6.4)	16 (5.7)
CD4 Cell Count (cells/microL)		
Mean (SD)	218.9 (124.2)	217.4 (133.6)
Median (min, max)	212.0 (1 to 620)	204.0 (4 to 807)
≤ 50 cells/µL, n (%)	27 (9.6)	31 (11.0)
> 50 but ≤ 200 cells/µL, n (%)	104 (37.0)	105 (37.2)
> 200 cells/µL, n (%)	150 (53.4)	145 (51.4)
Plasma HIV RNA (copies/mL)		
Geometric Mean	103205	106215
Median (min, max)	114000 (400 to 750000)	104000 (4410 to 750000)
≤ 100,000 copies/mL, n(%)	127 (45.2)	139 (49.3)
> 100,000 copies/mL, n (%)	154 (54.8)	143 (50.7)
Viral Subtype n (%)		
Clade B	219 (77.9)	230 (81.6)
Non-Clade B	59 (21.0)	47 (16.7)
Missing	3 (1.1)	5 (1.8)

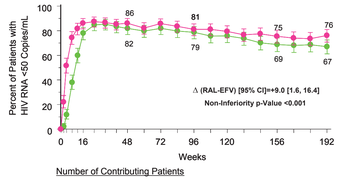
† Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C Virus.

Proportion of Patients with HIV RNA < 50 copies/mL (NC=F)

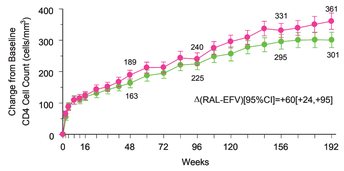
Time Point	Raltegravir n/N (%)	Efavirenz n/N (%)	Treatment Difference‡ % (95% CI)
Week 48	241/280 (86.1)	230/281 (81.9)	4.2 (-1.9, 10.3)
Week 96	228/281 (81.1)	222/282 (78.7)	2.4 (-4.3, 9.0)
Week 144	217/280 (77.5)	197/281 (70.1)	7.3 (0.0, 14.5)
Week 192	214/281 (76.2)	189/282 (67.0)	9.0 (1.6, 16.4)

‡95% CIs and p-values for non-inferiority for treatment differences in percent response were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screen HIV RNA>50,000 copies/mL or ≤ 50,000 copies/mL). Raltegravir is considered non-inferior to Efavirenz if the lower bound of the 95% CI for the difference in percent response is above -12 percentage points. It can be further concluded that Raltegravir is superior to Efavirenz if the lower bound exceeds zero.

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



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



Summary of Efficacy at Week 192

Treatment Group	Proportion of Patients (%, n/N) with HIV RNA < 50 copies/mL*			CD4 Cell Count, Change from BL (cells/mm³)
	NC=F	TRD=F	OF	OF‡
RAL (N=281)	76.2 (214/281)	86.3 (214/248)	91.1 (214/235)	360.7
EFV (N=282)	67.0 (189/282)	76.2 (189/248)	85.1 (189/222)	300.9
RAL - EFV†§	9.0* (1.6, 16.4)	10.1* (3.3, 17.0)	6.0* (0.1, 12.2)	59.8 (24.1, 95.4)

† 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.
§ BL values carried forward for virologic failures.

Cumulative Resistance at Week 192

Raltegravir group (N=281)	FTC Sensitive (12)	FTC Resistant (6)	TDF Sensitive (18)	TDF Resistant (0)	RT not amplified (3)
RAL Sensitive (12)	9	1	10	0	2
RAL Resistant (4)*	0	3*	3	0	1
IN not amplified (5)	3	2	5	0	0

*4/281 (1.4%) developed proven IN resistance
3/281 (1.1%) developed proven dual INRTI resistance

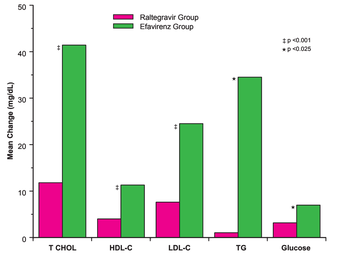
Efavirenz group (N=282)	FTC Sensitive (9)	FTC Resistant (5)	TDF Sensitive (13)	TDF Resistant (1)	RT not amplified (3)
EFV Sensitive (7)	5	2	7	0	0
EFV Resistant (7)*	4	3*	6	1*	0
RT not amplified (3)	0	0	0	0	3

*7/282 (2.5%) developed proven NNRTI resistance
3/282 (1.1%) developed proven dual NNRTI/RTI resistance

Interval Resistance Data from Week 156 to Week 192

- Between Weeks 156 and 192, there were 4 new patients (3 in the RAL group and 1 in the EFV group) who met the protocol definition of virologic failure
  - 1/4 patients (1 in the RAL group and 0 in the EFV group) had vRNA >400c/mL and evaluable resistance data
- 0/1 patients with evaluable data in the RAL group had detectable resistance to any of the drugs in their regimen
- No patient in the RAL group has failed with detectable resistance to RAL since Week 96
- 2 patients in the EFV group have failed with detectable resistance to EFV since Week 96

Mean Change from Baseline† in Metabolic Parameters at Week 192



- The change from baseline in the Total CHOL:HDL-C ratio was -0.17 for the RAL group and 0.02 for EFV group (p=0.177).

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

Number (%) of Patients with Selected Laboratory Abnormalities at Week 192

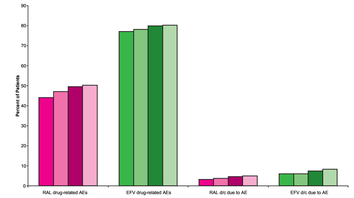
Laboratory Test	PDLC Criteria	Grade	Number (%) with PDLC: RAL 400 mg BID (N=281) n/m (%)	Number (%) with PDLC: EFV 600 mg qhs (N=282) n/m (%)
Blood Chemistry Test				
Fasting LDL-C (mg/dL)	160 – 189	Grade 2	21/271 (7.7)	32/262 (12.2)
	≥190	Grade 3	5/271 (1.8)	25/262 (9.5)
Fasting Cholesterol (mg/dL)	240 – 300	Grade 2	27/276 (9.8)	47/267 (17.6)
	>300	Grade 3	0/276 (0)	17/267 (6.4)
Fasting Triglycerides (mg/dL)	500 -750	Grade 2	3/276 (1.1)	12/267 (4.5)
	751-1200	Grade 3	1/276 (0.4)	4/267 (1.5)
	>1200	Grade 4	0/276 (0.0)	4/267 (1.5)
Fasting Glucose (mg/dL)	126 – 250	Grade 2	13/274 (4.7)	15/266 (5.6)
	251 – 500	Grade 3	5/274 (1.8)	2/266 (0.8)
	>500	Grade 4	0/274 (0.0)	0/266 (0.0)
Total Bilirubin (mg/dL)	1.6 – 2.5 ×ULN	Grade 2	13/281 (4.6)	0/279 (0.0)
	2.6 – 5.0 ×ULN	Grade 3	2/281 (0.7)	0/279 (0.0)
Creatinine (mg/dL)	1.4 – 1.8 x ULN	Grade 2	2/281 (0.7)	2/279 (0.7)
	1.9 – 3.4 x ULN	Grade 3	0/281 (0.0)	1/279 (0.4)
	≥3.5 x ULN	Grade 4	0/281 (0.0)	0/279 (0.0)
Aspartate aminotransferase (IU/L)	2.6 – 5.0 x ULN	Grade 2	16/281 (5.7)	23/279 (8.2)
	5.1 – 10.0 x ULN	Grade 3	12/281 (4.3)	8/279 (2.9)
	>10.0 x ULN	Grade 4	3/281 (1.1)	1/279 (0.4)
Alanine aminotransferase (IU/L)	2.6 – 5.0 x ULN	Grade 2	29/281 (10.3)	31/279 (11.1)
	5.1 – 10.0 x ULN	Grade 3	4/281 (1.4)	5/279 (1.8)
	>10.0 x ULN	Grade 4	4/281 (1.4)	2/279 (0.7)
Alkaline phosphatase (IU/L)	2.6 – 5.0 x ULN	Grade 2	3/281 (1.1)	9/279 (3.2)
	5.1 – 10.0 x ULN	Grade 3	0/281 (0.0)	1/279 (0.4)
	>10.0 x ULN	Grade 4	1/281 (0.4)	1/279 (0.4)

Only patients with a worsened grade from baseline were included in this analysis. ULN, upper limit of normal.
No Grade 4 events were reported for fasting LDL-C, fasting cholesterol, or total bilirubin.

Clinical Adverse Events

- Overall clinical AEs: RAL 269 (95.7%) vs. EFV 276 (97.9%), p=0.160
- Drug-related clinical AEs: RAL 141 (50.2%) vs. EFV 226 (80.1%), p<0.001
- Patients discontinued due to clinical AE: RAL 14 (5.0%) vs. EFV 23 (8.2%), p=0.173
- Serious clinical AEs: RAL 50 (17.8%) vs. EFV 52 (18.4%), p=0.913
  - Deaths (cumulative): RAL 5 (1.8%) vs. EFV 2 (0.7%)
    - Cause of death: Kaposi's sarcoma, lung CA (x2), drug toxicity/alcohol poisoning, and cerebral hemorrhage in RAL group; sepsis and unknown (not reported) in EFV group
    - 3 patients died since Week 156: 1 in RAL group (lung CA) and 2 in EFV group (sepsis and cause unknown)
    - None of the deaths were considered drug related
  - 14 new serious clinical AEs between Week 156 and 192
    - 7 in RAL group: migraine (x2), depression, meningitis, basal cell carcinoma, Kaposi's sarcoma, back pain
    - 7 in EFV group: lymphoma, endometritis, death, pancreatitis, anemia, mononucleosis, tuberculosis
    - One new SAE (pancreatitis) was considered possibly related to EFV (alone or in combination with TDF/FTC)

Percent of Patients with Drug-related Clinical AE or Discontinued due to Clinical AE



Most Common Drug-Related† Clinical AEs

Clinical AE	RAL 400 mg BID (N = 281) n (%)	EFV 600 mg qhs (N = 282) n (%)
Diarrhea	14 (5.0)	27 (9.6)
Nausea	25 (8.9)	29 (10.3)
Fatigue	12 (4.3)	25 (8.9)
Dizziness	18 (6.4)	99 (35.1)
Headache	26 (9.3)	40 (14.2)
Abnormal dreams	19 (6.8)	37 (13.1)
Insomnia	19 (6.8)	23 (8.2)
Nightmares	8 (2.8)	15 (5.3)
Rash	3 (1.1)	23 (8.2)

†Determined by investigator to be possibly, probably, or definitely related to RAL or EFV alone or in combination with TDF/FTC; incidence >5% in either treatment group.

Conclusions

- After 4 years of treatment, RAL + TDF/FTC is associated with superior antiretroviral efficacy and CD4 responses vs EFV + TDF/FTC in treatment-naïve patients
  - HIV suppression <50 copies/mL maintained in 76.2% of RAL group vs 67.0% of EFV group [tx difference, 9.0% (95% CI, 1.6 - 16.4)]
  - Mean change from baseline in CD4 count was 361 for RAL group and 301 for EFV group [tx difference, 60 (95% CI, 24 - 95)]
- The long-term tolerability and metabolic profile of RAL + TDF/FTC remain favorable
  - Drug-related clinical AEs occurred less often with RAL than EFV
  - RAL was generally well tolerated with few discontinuations due to clinical AEs
  - At week 192, RAL had less impact on fasting lipids than EFV

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STARTMRK principal investigators by country: Australia: Cooper D; ***Brazil:*** Madruga J, Netto E, Zajdenverg R; ***Canada:*** Baril JG, Kovacs C, Smaill F; ***Chile:*** Allen A, Beltran C, Perez Godoy J; ***Colombia:*** Angela M, Arango A, Tamara J, Velez J; ***France:*** Cotte L, Girard P-M, Palcoux G, Salmon-Ceron D, Yazdanpanah, Y; ***Germany:*** Esser S, Fatkenheuer G, Rockstroh JK, Schmidt R, Stellbrink H-J; ***India:*** Dinaker M, Pazare A, Rajendran J, Srivastava O; ***Italy:*** Caros Viscoli C; ***Mexico:*** Andrade J, Quintero Perez N, Reyes G, Sierra J, Torres I; ***Peru:*** Gotuzzo E, Lama J, Cabello-Chavez R, Salazar R; ***Spain:*** Portilla Sogorb J, Rivero-Roman A, Santamaria Jauregui J; ***Thailand:*** Manosuthi W, Sungkanuparph S, Supparatpinyo K, Vibhagool A; ***United States:*** Berger D, DeJesus E, Friel T, Hicks C, Kozal M, Kumar P, Lennox J, Liporace R, Little S, Morales-Ramirez J, Novak R, Pollard R, Saag M, Santiago S, Schneider S, Steigbigel R, Towner W, Wright D