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

#H924b
ICAAC
San Francisco, CA
September 2009

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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/mm³[†‡]	
	48-week	96-week	48-week	96-week
RAL (N=280, 281)	86	81	189 (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

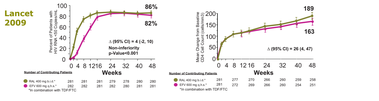
Conclusion: In treatment-naïve patients, RAL+TDF/FTC had durable, non-inferior antiretroviral activity sustained to 96-weeks compared to EFV+TDF/FTC & continued to be generally well tolerated.

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

Lancet 2009



- 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

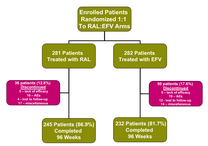
Main Hypotheses

- 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:
    (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.
- 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

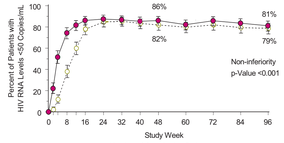


Baseline Characteristics

	RAL Group	EFV Group
# 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 >10⁵ 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

Results

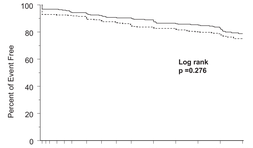
Proportion (%) of Patients (95% CI) With HIV RNA <50 c/mL Through 96 Weeks (Non-Completer = Failure)



● RAL mg b.i.d.	281	281	281	279	278	280	280	281	281	280	281
○ EFV 600 mg q.h.s.	282	282	281	282	280	281	281	282	282	281	282

- 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

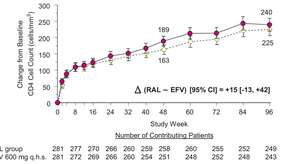
Time to Loss of Virologic Response (HIV RNA ≥50 c/mL)



RAL 400 mg b.i.d.	281	272	266	264	259	255	254	250	243	239	210	117
EFV 600 mg q.h.s.	282	261	260	256	249	246	241	236	232	226	196	110

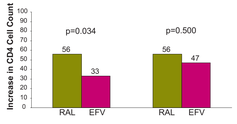
- The time to *achieve* virologic response was significantly shorter for patients in RAL group compared to the EFV group (log-rank test p-value of 0.001).

Change from Baseline in CD4 Cell Count



● RAL group	281	277	270	266	260	259	258	260	255	252	249
○ EFV 600 mg q.h.s.	281	272	269	266	260	254	251	248	252	248	243

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: RAL[§] (6 were FTC[¶], TDF[¶], 2 did not amplify FTC or TDF)
      - 4 patients: RAL[§*] (3 were FTC[¶], TDF[¶] ; 1 did not amplify FTC or TDF)
      - 4 patients: RAL could not be amplified (2 were FTC[¶], TDF[¶]; 2 were FTC[¶], TDF[¶])

* 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: EFV[‡] (FTC[¶], TDF[¶])
      - 5 patients: EFV[‡*] (2 were FTC[¶], TDF[¶]; 3 were FTC[¶], TDF[¶])
      - 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)**
Diarrhoea	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)
Pyrexia	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	(-10.8, -0.6)
Insomnia	34	(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	159 (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 ANOCOVA 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**

Acknowledgements

STARTMRK Study Team

Investigators

D.S. Berger, E. DeJesus, T.J. Friel, C.B. Hicks, M.J. Kozal, P.N. Kumar, J. Lennox, S. Little, C. Del Rio, R.L. Liporace, J.O. Morales-Ramirez, R.M. Novak, R.B. Pollard, M.S. Saag, S. Santiago, S. Schneider, R.T. Steigbigel, W.J. Towner, D.P. Wright, G. Carosi, C. Viscoli, A. Lazzarin, A. Chirianni, R. Esposito, C. Kovacs, G.H.R. Smith, S. Esser, G. Fatkenheuer, J. Rockstroh, M.J. Stellbrink, R.E. Schmidt, J. Sierra, J. Andrade, N. Quintero, G. Reyes, I. Torres, G. Pialoux, Y. Yazdanpanah, C. Cotte, K. Salmon-Ceron, P.M.Girard, D. Cooper, C. Beltrán, A. Afani, J. Pérez, J.M. Santamaria Jauregui, J. Portilla Segorb, A. Rivero Roman, F. Smaill, S. Sungkanuparph, A. vibhagool, W. Manosuthi, K. Supparatpinyo, J.G. Baril, R. Zajenverg, J.V.R. Madruga, E. Martins Netto, J.D. Velez, J.R. Tamara, A.I. Arango, A.M. Tobon, M.R. Salazar Castro, J.E. Gotuzzo Herencia, R.L. Cabello Chávez, J.R. Lama Valdivia, O.P. Srivastava, J. Rajendran, A.R. Pazare, M. Dinakare

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