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Sustained Antiretroviral Efficacy of Raltegravir after 192 Weeks of Combination ART in Treatment-Naive HIV-1 Infected Patients

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Abstract

Objectives: Phase II study evaluating long term efficacy, safety and tolerability of raltegravir (RAL), an HIV-1 integrase inhibitor, vs efavirenz (EFV), combined with tenofovir/lamivudine (TDF/3TC), in ART-naive HIV-1-infected patients (pts).

Methods: Multicenter, double-blind, randomized study evaluating RAL 400mg bid (after 100, 200, 400 or 600mg bid for first 48 weeks) vs EFV 600mg qd, both with TDF/3TC, in ART naive pts with HIV-1 RNA ≥5000 copies/mL and CD4+ T-cells ≥100/uL. This abstract presents complete 192 week data. Exploratory analyses investigated the potential relationship between early virologic response and long term CD4 response.

Results: 198 pts were randomized and treated; 160 pts received RAL and 38 received EFV. Baseline information and dose-ranging results to week 144 have been presented previously. At week 192, 75% of RAL pts vs 74% of EFV pts sustained HIV-1 RNA <400 copies/mL; 74% of both groups sustained <50 copies/mL (non-completer=failure). RAL and EFV groups showed similar increases in CD4+ T-cells (295 vs 274/uL, respectively). One pt in the EFV group and none in the RAL group met the protocol definition of virologic failure after week 144. Cumulative rates of drug-related clinical adverse events (AEs) remained less frequent in the RAL vs EFV group (55% vs 76%, respectively). Drug-related AEs occurring in >10% of total pts were nausea (RAL 13%, EFV 11%), dizziness (9%, 26%), and headache (9%, 24%). Grade 3 and 4 laboratory abnormalities remained infrequent, generally ≤5% in the RAL group and ≤8% in the EFV group. RAL had minimal effect on total or LDL cholesterol, or triglycerides. Cumulative neuropsychiatric AEs remained less frequent with RAL (38%) than EFV (63%). There were no drug-related serious AEs in pts receiving RAL. Exploratory analyses showed that the change in CD4 count at week 192 was predicted by week 8 vRNA decrease: each vRNA log decline at week 8 yielded additional 145 and 131 cell increases at week 192 for RAL and EFV, respectively.

Conclusions: In ART-naive pts, RAL with TDF/3TC had potent and durable antiretroviral activity, drug-related AEs were less frequent in pts treated with RAL compared to EFV.

Background

- Raltegravir (RAL) is now approved for use in combination regimens for the treatment of HIV infection[1].
- Week 96 data from Phase III studies in treatment-naïve[2] and treatment-experienced[3] patients have demonstrated potent efficacy and good overall tolerability.
- Protocol 004 (P004) is a Phase II study of RAL vs efavirenz (both with tenofovir/3TC) in treatment-naïve patients that has demonstrated sustained efficacy and good general tolerability up to Week 144[4].
- This poster presents updated P004 data to Week 192, including:
  - Exploratory analysis: Relationship between early viral load decline and long-term change in CD4 counts

Methods

Study Design

- Key inclusion criteria
  - No prior ART
  - HIV RNA ≥ 5000 copies/mL and susceptible to EFV, TDF, 3TC
  - CD4 ≥ 100 cells/mm
- Hypothesis: RAL + TDF/3TC will be generally well tolerated, with similar antiretroviral activity vs EFV + TDF/3TC

Overall Analysis

- Endpoints:
  - HIV RNA, CD4 counts, Adverse events
  - Exploratory: CNS adverse events, change in serum lipids
- Timepoints:
  - Week 24 primary, Weeks 48 and 96 secondary
  - Weeks 144 and 192 are exploratory
- Dosing:
  - Week 0-48 was dose ranging:
    - RAL given at 100, 200, 400 or 600 mg b.i.d.
    - Doses could not be differentiated at 48 weeks
  - After 48 weeks, all RAL groups received 400 mg b.i.d.
  - Therefore, all RAL data post-48 weeks shown as single group (N=160)

Exploratory Analysis

- Rationale: earlier HIV suppression by RAL vs EFV observed in P004 and P021[5] but of unclear significance
- Relationship between early decrease in HIV RNA and later increase in CD4-cell count explored using observed failure (OF) approach
  - A linear regression model of CD4 cell count at each time point (Week 48, 96, 144 and 192) included the following among model predictors:
    - Baseline CD4 cell count
    - Week 8 HIV RNA log decrease
    - Treatment group

Results

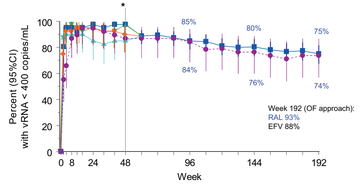
Baseline Characteristics / Patient Status

	RAL *	EFV *
Baseline Characteristics		
# Patients Treated	N = 160	N = 38
Mean age (yrs)	36	36
% Male	80	76
% Non-White	69	68
HIV RNA copies/ml** (log10cp/ml)	55266 (4.7)	67554 (4.8)
Mean CD4 count (cells/ul)	305	280
% with AIDS†	34	37
Patient Status		
Discontinuations by Week 192	40 (25%)	10 (26%)
Lack of efficacy	4 (2.5%)	2 (5.3%)
Adverse event	4 (2.5%)	1 (2.6%)
Withdrew consent	9 (5.6%)	4 (10.5%)
Lost to follow-up	7 (4.4%)	1 (2.6%)
Other reasons	16 (10.0%)	2 (5.3%)

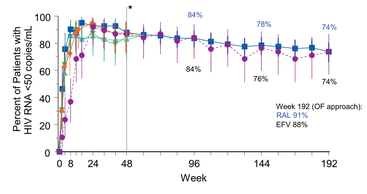
* With TDF/3TC, **geometric mean, †Defined as history of clinical diagnosis of AIDS at baseline.

Efficacy Analysis

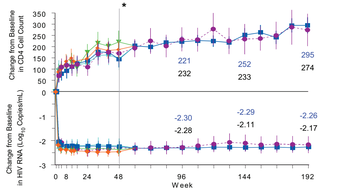
Patients with HIV RNA <400 copies/mL (NC=F†)



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



Change from Baseline: CD4 and HIV RNA (OF‡)



‡Observed Failure (OF) approach: only discontinuations due to lack of efficacy are counted as failures.

Number of Contributing Patients (NC=F† Approach)

	Week					
	0	24	48	96	144	192
Raltegravir 100 mg b.i.d.	39	39	39			
Raltegravir 200 mg b.i.d.	40	40	40			
Raltegravir 400 mg b.i.d.	41	41	41	159	158	160
Raltegravir 600 mg b.i.d.	40	40	40			
Efavirenz 600 mg b.i.d.	38	37	38	38	38	38

*After Week 48 patients in all RAL groups continued at 400 mg b.i.d. All patients also received TDF/3TC.
†Non-completer equals failure (NC=F) approach treats all discontinuations as failures.

- After Week 144 there were no new virologic failures (relapses) on RAL and 1 failure on EFV.
  - Patient had HIV RNA ≤300 copies/mL so resistance testing was not performed

Safety Analysis

Safety Summary: Week 192

- Overall adverse event (AE) profiles generally similar for RAL and EFV
  - Similar frequencies reported at Weeks 144[4] and 192
- Drug-related clinical AEs: RAL 55% vs EFV 76%
- Neuropsychiatric symptoms*:
  - Most occurred by Week 48
  - At Week 192 : 38% for RAL vs 63% for EFV
- Malignancies†: 2.5% (4/160 pts) for RAL vs. 2.6% (1/38 pts) for EFV
- Grade 3 / 4 lab abnormalities uncommon
  - Similar frequencies reported at Weeks 144[4] and 192
- Minimal effect of RAL on serum lipids

*Abnormal dreams, acute psychosis, adjustment disorder with depressed mood, auditory hallucination, completed suicide, concentration impaired, confusional state, delirium, depressed level of consciousness, depressed mood, depression, depressive symptom, dizziness, dysthymic disorder, hallucination, hallucination visual, insomnia, major depression, nervous system disorder, nightmare, psychotic disorder, somnolence, suicidal behavior, suicidal ideation, suicide attempt.
† Cases included: 1 pt with B-cell lymphoma, 2 pts with Kaposi's sarcoma, 1 pt with both basal cell carcinoma and squamous cell carcinoma (SC), 1 pt with both gastrointestinal carcinoma and SC

Most Common* Drug-Related Adverse Events (Weeks 144 and 192)

	Week 144		Week 192	
	RAL (N=160) %	EFV (N=38) %	RAL (N=160) %	EFV (N=38) %
Diarrhea	6.9	10.5	6.9	10.5
Nausea	12.5	10.5	13.1	10.5
Dizziness	8.8	26.3	8.8	26.3
Headache	8.8	23.7	8.8	23.7
Abnormal Dreams	6.3	18.4	6.3	18.4
Insomnia	8.1	10.5	8.1	13.2
Nightmares	0	10.5	0	10.5

RAL taken twice daily; EFV taken once daily; both with TDF/3TC.
* Incidence at least 10% in either treatment group; all intensity levels included.

Grade 3/4† Laboratory Abnormalities (Weeks 144 and 192)

Laboratory Test	Toxicity Criteria	Week 144 RAL (N=160) %	Week 144 EFV (N=38) %	Week 192 RAL (N=160) %	Week 192 EFV (N=38) %
Absolute neutrophil count	<750 cells/µL	1.3	0.0	1.3	0.0
Fasting LDL cholesterol	≥190 mg/dL	0.6	5.3	1.3	5.7
Fasting total cholesterol	>300 mg/dL	0.0	5.3	1.3	8.1
Fasting triglycerides	>750 mg/dL	0.6	7.9	1.3	8.1
Fasting glucose	>250 mg/dL	0.6	0.0	0.6	0.0
Alkaline phosphatase	>5 x ULN	0.6	0.0	0.6	0.0
Pancreatic amylase	>2 x ULN	2.5	0.0	3.8	0.0
Lipase	>3 x ULN	1.3	0.0	1.3	0.0
Aspartate aminotransferase	>5 x ULN	3.8	2.6	3.8	5.3
Alanine aminotransferase	>5 x ULN	2.5	5.3	3.1	5.3
Creatine kinase	≥10 x ULN	8.8	2.6	8.8	5.3

†Division of AIDS grading scale December 2004
ULN – Upper Limit of Normal

No grade 3 or 4 abnormalities were reported in either treatment group for the following parameters: hemoglobin, platelet count, creatinine, and total bilirubin.

Serum Lipids: Mean Change from Baseline (mg/dL) at Week 192

	RAL (N=160)		EFV (N=38)		
	Baseline Mean	Mean Change (SD)	Baseline Mean	Mean Change (SD)	RAL vs EFV
Cholesterol	166.7	10.3 (32.9)	171.1	47.7 (92.4)	P=0.044
LDL-C	104.3	0.3 (29.6)	110.1	8.9 (20.1)	P=0.072
HDL-C	38.0	6.5 (8.6)	38.1	14.6 (10.2)	P<0.001
Triglycerides	132.8	10.9 (83.7)	115.0	177.1 (821)	P=0.294
Total: HDL ratio	4.6	-0.5 (1.3)	4.6	-0.2 (2.43)	P=0.621

In the RAL group:

- LDL-cholesterol and triglycerides were not increased
- Total cholesterol showed a small increase, mainly due to HDL-C

Exploratory Analysis

Prognostic Factors Associated with CD4 Response at Yearly Time Points

Prognostic Factor	P-value† Week 48	Week 96	Week 144	Week 192
Baseline CD4 cell count (cells/mm³)	<0.0001	<0.0001	<0.0001	<0.0001
Week 8 HIV RNA decline (log_{10} copies/mL)	0.0005	<0.0001	<0.0001	<0.0001
Treatment Group	0.2887	0.3592	0.9778	0.6421

†p-Value was calculated from a linear regression model with CD4 cell count separately at each time point as the dependent variable adjusted for baseline CD4 cell count (c/mm3), Week 8 HIV RNA Decline (log10 copies/mL) and treatment group.

- Significant predictors for CD4 response (at 0.05 critical value) at each time point were baseline CD4 count and log drop in week 8 HIV RNA level.

Conclusions

- **RAL + TDF/3TC demonstrated sustained antiretroviral efficacy at 192 weeks similar to EFV + TDF/3TC:**
  - **74% in both groups had HIV RNA < 50 copies/mL**
  - **CD4 counts continue to increase through week 192 in both groups**
- **RAL was generally well tolerated at Week 192:**
  - **Safety profile similar to Week 144**
  - **Drug-related AEs less frequent for RAL vs. EFV**
  - **RAL had minimal effect on LDL-cholesterol and triglycerides.**
- **In an exploratory analysis, statistically significant predictors for the CD4 response at each yearly time point were baseline CD4 count and log drop in HIV RNA at week 8.**

References

1. ISENTRESS (raltegravir) product information, 2009.
2. Lennox et al. ICAAC 2009 [abstract H-924b].
3. Steigbigel et al., Clin Infect Dis 2010;50:605-12.
4. Gotuzzo et al. 28th International AIDS Conference 2009 [abstract A-155-0079-01895].
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