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Doravirine 100 mg QD vs Efavirenz +TDF/FTC in ART-Naïve HIV+ Patients: Week 48 Results

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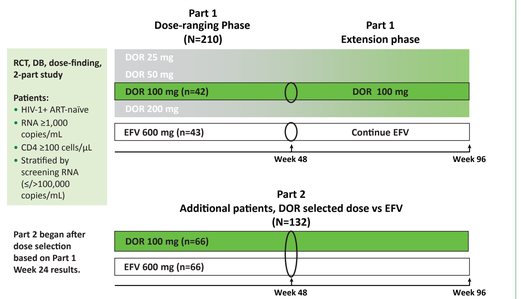
Background

- Commonly used non-nucleoside reverse transcriptase inhibitors (NNRTIs) are associated with suboptimal efficacy and/or safety profiles
  - Efavirenz – Frequent CNS adverse events[1]; no longer recommended as first-line therapy for HIV infection in multiple guidelines[1-3]
  - Rilpivirine – Treatment-naïve indication only for RNA ≤100,000 copies/mL in US[1] and EU[2]
- Doravirine (DOR, aka MK-1439) is a novel NNRTI
  - High in vitro potency vs broad panel of isolates, including common NNRTI-resistant variants[4]
  - Primary metabolism by CYP3A4; not an inducer or inhibitor[5]
  - Once-daily dosing (without regard to food)
  - No interactions expected with proton pump inhibitors
- In Part 1 of this Phase 2 study (MK-1439 Protocol 007):
  - Antiretroviral activity of DOR 25, 50, 100, and 200 mg QD with tenofovir/emtricitabine (TDF/FTC) was similar to efavirenz (EFV) with TDF/FTC at Week 24[6] and Week 48[7]
  - Safety profile of DOR was favorable at all doses
  - DOR 100 mg was selected for Part 2 and for evaluation in the Phase 3 program

Protocol 007 Study Schema



Statistical Analysis

- **Populations analyzed**
  - Patients randomized to DOR 100 mg or EFV 600 mg, both given with TDF/FTC
    - DOR 100 mg: Part 1 (n=42) + Part 2 (n=66); total=108 patients
    - EFV 600 mg: Part 1 (n=43) + Part 2 (n=66); total=109 patients
  - Full Analysis Set (efficacy): All randomized patients who had at least 1 postrandomization observation after receiving at least 1 dose of blinded study treatment
  - All Patients as Treated (safety): All randomized patients who received at least 1 dose of study treatment
- **Efficacy endpoints**
  - Virologic response: Proportion of patients with HIV RNA <40 copies/mL (primary), with HIV RNA <200 copies/mL (secondary)
    - Noncompleter = Failure (NC=F) approach for missing data
  - Immunologic response: Change from baseline in CD4 count
    - Observed Failure (OF) approach for missing data
  - Virologic response by screening HIV RNA (≤ vs >100,000 copies/mL)
    - OF approach for missing data: Missing values imputed as failure for (1) discontinuation due to lack of efficacy and (2) discontinuation for non-treatment-related reasons, if final vRNA is >40 copies/mL
- **Safety endpoints**
  - Clinical adverse events: Collected through 14 days post-treatment
  - Laboratory parameters: Predefined limits of change, DAIDS toxicity criteria

Results

Patient Status, Week 48

	DOR 100 mg	EFV 600 mg
Patients randomized, n	108	109
Patients treated, n	108	108
Patients discontinued, %	12.0	14.7
Adverse event	2.8	5.5
Lack of efficacy	0.0	0.9
Lost to follow-up	2.8	3.7
Noncompliance with study drug†	4.6	0.0
Physician decision	0.0	0.9
Withdrawal by subject	1.9	3.7

Calculation of percentages based on number of patients randomized.
†Physician decision to discontinue patient based on failure to comply with dosing requirements of the study; does not include discontinuation due to an adverse event.

Baseline Patient Characteristics

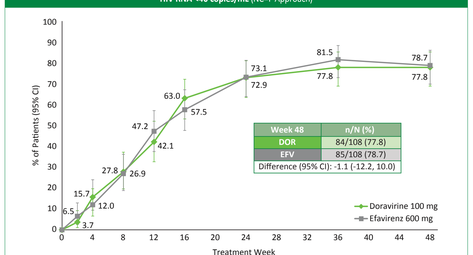
Treated patients	DOR 100 mg N=108	EFV 600 mg N=108
% male	91.7	93.5
Age (years), median (range)	35 (19 – 67)	34 (20 – 57)
% white	79.6	79.6
% with AIDS	3.7	6.5
HIV RNA (log_{10} copies/mL), median (range)	4.6 (2.6 – 6.5)	4.6 (3.0 – 6.7)
% with HIV RNA >100,000 copies/mL, at screening	35.2	37.0
CD4 count (cells/μL), median (range)	402 (92 – 1110)	430 (118 – 1121)
% with CD4 count ≤200 cells/μL	6.5	9.3
% with Clade B viral subtype	69.4	79.6

Summary of Week 48 Outcomes (NC=F Approach)†

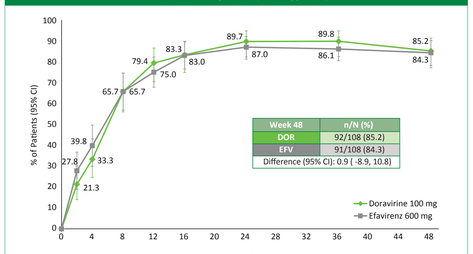
	DOR 100 mg (N=108)		EFV 600 mg (N=108)	
	n	(%)	n	(%)
Success (HIV RNA <40 copies/mL) at Week 48	84	(77.8)	85	(78.7)
Nonsuccess at Week 48	24	(22.2)	23	(21.3)
HIV RNA ≥40 copies/mL	18	(16.7)	14	(13.0)
≥40 and <200 copies/mL	8	(7.4)	6	(5.6)
≥200 copies/mL	3	(2.8)	2	(1.9)
Discontinued study due to lack of efficacy or discontinued for other reasons, with last HIV RNA ≥40 copies/mL‡	7	(6.5)	6	(5.6)
No virologic data at Week 48 window	6	(5.6)	9	(8.3)
Discontinued study due to AE or death	3	(2.8)	6	(5.6)
Discontinued study for other reasons, with last HIV RNA <40 copies/mL	3	(2.8)	2	(1.9)
On study but missing data in Week 48 window	0	(0.0)	1	(0.9)

†Overall success/nonsuccess rates are identical for NC=F and the FDA snapshot approach.
‡Majority of patients in this category (5 of 7 in DOR group; 4 of 6 in EFV group) had last HIV RNA >200 copies/mL.
No treatment-emergent resistance mutations were detected in the 4 patients (3 DOR, 1 EFV) who had HIV RNA >500 copies/mL at the time of virologic failure. Another patient who failed on DOR had a sample tested for resistance 1 month later: new NNRTI mutations (E138E/G + V179D) were present, with no change in phenotypic sensitivity (0.75 fold change) to DOR and 7.14 fold decreased susceptibility to EFV.

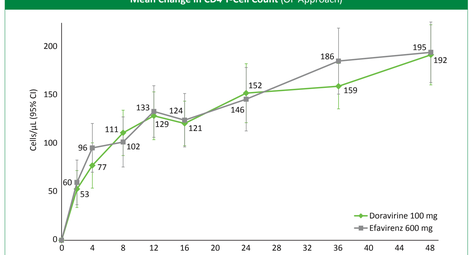
HIV RNA <40 copies/mL (NC=F Approach)



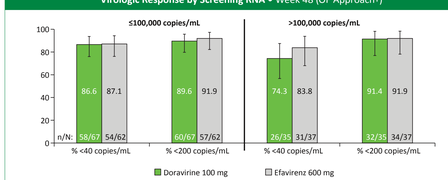
HIV RNA <200 copies/mL (NC=F Approach)



Mean Change in CD4 T-Cell Count (OF Approach)



Virologic Response by Screening RNA • Week 48 (OF Approach†)



†Excludes patients who (1) discontinued due to AE, (2) discontinued due to non-treatment-related reasons and had last RNA <40 copies/mL, or (3) were on study but missing data in Week 48 window.

Clinical Adverse Events (%)

	DOR 100 mg (N=108)	EFV 600 mg (N=108)	Difference [DOR – EFV] (95% CI)
One or more adverse events (AE)	**87.0**	**88.9**	**-1.9 (-10.9, 7.1)**
Serious AE†	6.5	8.3	-1.9 (-9.5, 5.6)
Death	0	0	
Discontinued due to AE	2.8	5.6	-2.8 (-9.2, 3.0)
Drug-related‡ AE	31.5	56.5	-25.0 (-37.3, -11.8)
Diarrhea	0.9	6.5	–
Nausea	7.4	5.6	–
Dizziness	6.5	25.9	–
Headache	2.8	5.6	–
Abnormal dreams	5.6	14.8	–
Insomnia	6.5	2.8	–
Nightmares	5.6	8.3	–
Sleep disorder	4.6	6.5	–

†Two serious AEs in the EFV group were considered drug-related: depression (1) and dizziness (1).
‡Determined by investigator to be related to study therapy; specific AEs with >5% incidence are listed.
Specific AEs causing discontinuation (n): DOR – hallucination (1), B-cell lymphoma (1), Hodgkin's disease (1); EFV – dysaesthesia (1), hallucinations (2), drug eruption (1), dizziness (1), disturbance in attention (1).

Common† Laboratory Abnormalities (%)

Laboratory Test	Grade (criteria)	DOR 100 mg (N=108)	EFV 600 mg (N=108)	Difference [DOR – EFV] (95% CI)
Absolute neutrophil count	1 (1.0-1.3 10^3/μL)	7.5	5.6	1.9 (-5.1, 9.3)
LDL-cholesterol, fasting	1 (130 – 159 mg/dL)	2.9	15.5	-12.6 (-21.2, -5.1)
	2 (160-189 mg/dL)	2.0	3.9	-1.9 (-7.9, 3.5)
Total cholesterol, fasting	1 (200 – 239 mg/dL)	5.8	20.2	-14.4 (-23.9, -5.6)
	2 (240 – 300 mg/dL)	0	6.7	-6.7 (-13.3, -3.0)
Glucose, fasting	1 (110 – 125 mg/dL)	9.6	11.0	-1.4 (-10.8, 7.7)
Bilirubin, total	1 (1.1 – 1.5 x ULN)	5.6	0.9	4.7 (-0.1, 10.9)
Aspartate aminotransferase	1 (1.25 – 2.5 x ULN)	9.3	12.0	-2.7 (-11.4, 5.9)
	2 (2.6 – 5.0 x ULN)	0.9	3.7	-2.8 (-8.3, 1.8)
Alanine aminotransferase	1 (1.25 – 2.5 x ULN)	7.5	12.0	-4.6 (-13.0, 3.6)
Alkaline phosphatase	1 (1.25 – 2.5 x ULN)	1.9	6.5	-4.6 (-11.2, 0.9)
Lipase	1 (1.1 – 1.5 x ULN)	11.2	9.3	2.0 (-6.5, 10.5)
	2 (1.6 – 3.0 x ULN)	4.7	7.4	-2.7 (-9.9, 4.1)
	3 (3.1 – 5.0 x ULN)	3.7	4.6	-0.9 (-7.2, 5.2)

†Occurred in at least 4 patients in one or more treatment groups, with indicated grade (based on DAIDS toxicity criteria), and was also an increase from baseline.

All Laboratory Abnormalities Grade ≥2 (%)

Laboratory Test	Grade (criteria)	DOR 100 mg (N=108)	EFV 600 mg (N=108)
Absolute neutrophil count	2 (0.75 – 0.999 x 10^3/μL)	1.9	1.9
	4 (<0.50 x 10^3/μL)	0	0.9
Platelet count	2 (50 – 99.9 x 10^3/μL)	0.9	0.9
LDL-cholesterol, fasting	2 (160 – 189 mg/dL)	2.0	3.9
	3 (≥190 mg/dL)	0	1.9
Total cholesterol, fasting	2 (240 – 300 mg/dL)	0	6.7
	3 (>300 mg/dL)	0	1.9
Triglycerides, fasting	2 (500 – 750 mg/dL)	0	1.9
Glucose, fasting	2 (126 – 250 mg/dL)	3.2	1.1
Aspartate aminotransferase	2 (2.6 – 5.0 x ULN)	0.9	3.7
	3 (5.1 – 10.0 x ULN)	0.9	0
	4 (>10.0 x ULN)	0	0.9
Alanine aminotransferase	2 (2.6 – 5.0 x ULN)	0.9	0
	3 (5.1 – 10.0 x ULN)	0.9	1.9
Lipase	2 (1.6–3.0 x ULN)	4.7	7.4
	3 (3.1 – 5.0 x ULN)	3.7	4.6
	4 (>5.0 x ULN)	0.9	1.9

Conclusions

In ART-naïve subjects with HIV-1 infection, doravirine 100 mg QD in combination with TDF/FTC:

- Demonstrates antiretroviral activity and immunological effect similar to efavirenz with TDF/FTC at Week 48
- Is safe and generally well tolerated through Week 48
  - Drug-related AEs were significantly less common in the DOR group (31.5%) vs the EFV group (56.5%)

Phase 3 trials of doravirine 100 mg QD are currently ongoing.

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