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Similar Efficacy and Safety By Subgroup in DRIVE-AHEAD: DOR/3TC/TDF vs EFV/FTC/TDF

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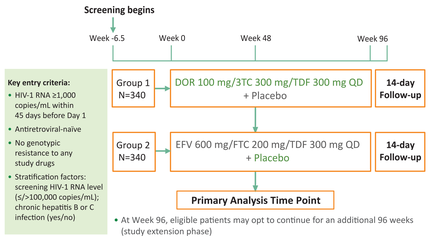
BACKGROUND

- Doravirine (DOR) is a novel, next-generation, HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI)
  - Unique resistance profile with in vitro activity against wild-type HIV-1 and the most prevalent NNRTI resistance mutations (RT K103N, Y181C, G190A, K103N/Y181C, and E138K)[1]
  - DOR 100 mg is taken once daily (QD) without regard to food[2]
  - Low potential for drug–drug interactions,[3] including with acid-reducing agents[4]
- Phase 3 DRIVE-AHEAD trial: co-formulated doravirine 100 mg, lamivudine 300 mg, and tenofovir disoproxil fumarate 300 mg (DOR/3TC/TDF) compared to co-formulated efavirenz 600 mg, emtricitabine 200 mg, and TDF 300 mg (EFV/FTC/TDF)[5]
  - Efficacy of DOR/3TC/TDF was non-inferior to EFV/FTC/TDF at Week 48
  - Safety of DOR/3TC/TDF was superior to EFV/FTC/TDF for neuropsychiatric events and change from baseline in LDL-C and non–HDL-C levels
- To further characterize the effects of DOR/3TC/TDF, Week 48 results from the DRIVE-AHEAD trial were examined by selected demographic and baseline clinical characteristics

METHODS

Trial Design

- DRIVE-AHEAD is a Phase 3, multicenter, double-blind, randomized, noninferiority study in treatment-naïve adults with HIV-1 infection



- At Week 96, eligible patients may opt to continue for an additional 96 weeks (study extension phase)

Statistical Analysis

- The primary endpoint was the proportion of participants with HIV-1 RNA <50 copies/mL at Week 48 using the FDA snapshot approach
  - All missing data were treated as failures regardless of the reason
  - The difference between treatment groups and associated 95% confidence interval (CI) were calculated using the stratum-adjusted Mantel-Haenszel method
  - DOR/3TC/TDF was considered non-inferior to EFV/FTC/TDF if the lower bound of the two-sided 95% CI was greater than -10 percentage points
- Efficacy results for pre-specified subgroups were examined using the Observed Failure Approach for missing data
  - Discontinuation due to lack of efficacy = failure; participants with missing data for other reasons were excluded from analysis
  - For CD4+ T-cell count, baseline values were carried forward for participants who discontinued due to lack of efficacy
- Safety and tolerability were evaluated by review of reported adverse events through Week 48

RESULTS

Trial Population

- Of the 734 participants assigned to DOR/3TC/TDF (n=368) or EFV/FTC/TDF (n=366), 364 in each group received at least one dose of study drug and were included in the analyses
- Demographics and baseline clinical characteristics were balanced across the treatment groups

Table 1. Baseline Characteristics

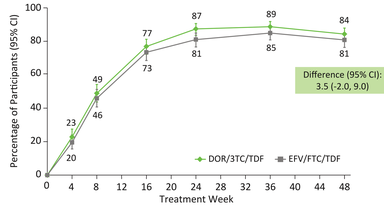
	DOR/3TC/TDF (N=364)	EFV/FTC/TDF (N=364)
Age (years), Median (range)	32.0 (18, 70)	30.0 (18, 69)
Male, n (%)	305 (83.8)	311 (85.4)
Race, n (%)		
White	177 (48.6)	170 (46.7)
Black or African American	67 (18.4)	68 (18.7)
Asian	59 (16.2)	65 (17.9)
Other[a]	61 (16.8)	61 (16.8)
Hispanic or Latino	126 (34.6)	120 (33.0)
Region, n (%)		
Africa	37 (10.2)	27 (7.4)
Asia/Pacific	59 (16.2)	62 (17.0)
Europe	88 (24.2)	94 (25.8)
Latin America	89 (24.5)	87 (23.9)
North America	91 (25.0)	94 (25.8)
CD4+ T-cell Count (cells/mm^3)		
Median (range)	414 (19, 1399)	388 (19, 1452)
≤50 cells/mm^3, n (%)	9 (2.5)	10 (2.7)
>50 and ≤200 cells/mm^3, n (%)	35 (9.6)	36 (9.9)
>200 cells/mm^3, n (%)	320 (87.9)	318 (87.4)
Plasma HIV-1 RNA		
Median (range), $\log_{10}$ copies/mL	4.4 (2.4, 6.1)	4.5 (2.6, 6.4)
≤100,000 copies/mL, n (%)	291 (79.9)	282 (77.5)
>100,000 copies/mL, n (%)	73 (20.1)	82 (22.5)
≤500,000 copies/mL, n (%)	354 (97.3)	346 (95.1)
>500,000 copies/mL, n (%)	10 (2.7)	18 (4.9)
History of AIDS, n (%)	46 (12.6)	53 (14.6)
Hepatitis B and/or C[b]	11 (3.0)	9 (2.5)
Viral Subtype, n (%)		
Subtype B	232 (63.7)	253 (69.5)
Subtype Non-B	130 (35.7)	111 (30.5)

[a]Other includes multiracial and American Indian or Alaska Native.
[b]Evidence of hepatitis B surface antigen or evidence of HCV RNA by PCR quantitative test.

Primary Analysis

- DOR/3TC/TDF was non-inferior to EFV/FTC/TDF on the primary endpoint, with HIV-1 RNA <50 copies/mL achieved by 84% and 81%, respectively, at Week 48 (difference 3.5%, 95% CI [-2.0, 9.0])

Figure 1. Proportion of Participants with HIV-1 RNA <50 copies/mL Over Time (FDA Snapshot Approach)



Subgroup Efficacy

- The proportion of participants with HIV-1 RNA <50 copies/mL at Week 48 was comparable between the treatment groups across all pre-specified baseline characteristics and demographic factors except age
  - Response rate appeared to favor EFV/FTC/TDF among younger participants (≤31 years), while favoring DOR/3TC/TDF among older participants (>31 years)
  - This finding is not consistent with the DRIVE-FORWARD Phase 3 DOR trial and is likely due to chance since the 95% CIs were not adjusted for multiple comparisons
- Similar results were observed for the virologic response endpoints of HIV-1 RNA <40 copies/mL and HIV-1 RNA <200 copies/mL (data not shown)
- Change from baseline in CD4+ T-cell count was comparable between the treatment groups for all prespecified baseline characteristics and demographic factors

Figure 2. Efficacy by Subgroup: Baseline Clinical Characteristics (Observed Failure Approach)

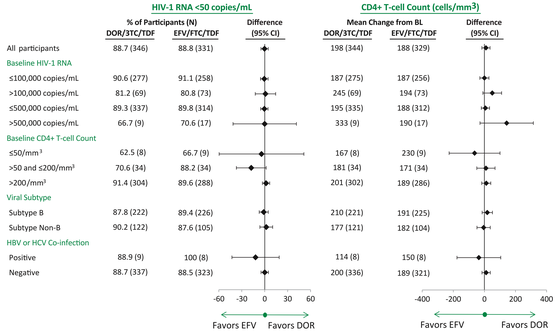
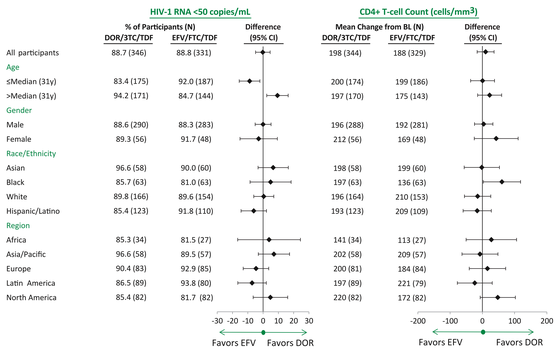


Figure 3. Efficacy by Subgroup: Demographic Factors (Observed Failure Approach)



Subgroup Safety

- Key safety findings of the overall trial were also observed across subgroups of gender, race/ethnicity, and baseline CD4+ T-cell count
  - Lower rates of drug-related AEs and discontinuation due to AEs in the DOR/3TC/TDF group
  - Lower rates of dizziness, abnormal dreams, and rash in the DOR/3TC/TDF group
- The number of participants with hepatitis B/C co-infection was very low, precluding meaningful interpretation of safety findings for this subgroup

Table 2. Clinical Adverse Events (%) by Gender*

	Male		Female	
	DOR/3TC/TDF N=305	EFV/FTC/TDF N=311	DOR/3TC/TDF N=59	EFV/FTC/TDF N=53
One or more AEs	83.6	91.0	78.0	88.7
Drug-related AEs	32.1	65.3	25.4	49.1
Serious AEs	3.6	5.8	3.4	5.7
Discontinued due to AE	3.0	6.4	3.4	7.5
Most Common AEs				
Abnormal dreams	5.2	13.2	1.7	1.9
Dizziness	9.2	38.6	6.8	28.3
Headache	12.5	12.9	15.3	9.4
Diarrhea	11.8	14.8	5.1	5.7
Nausea	7.5	10.6	8.5	11.3
Nasopharyngitis	11.5	9.0	6.8	5.7
Rash	4.9	12.5	3.4	9.4

*Percent of participants with AE in subgroup (n/N). N = number of participants in subgroup.

Table 3. Clinical Adverse Events (%) by Race/Ethnicity*

	Asian		Black or African American	
	DOR/3TC/TDF N=59	EFV/FTC/TDF N=65	DOR/3TC/TDF N=67	EFV/FTC/TDF N=68
One or more AEs	76.3	92.3	79.1	85.3
Drug-related AEs	30.5	73.8	23.9	44.1
Serious AEs	1.7	1.5	3.0	5.9
Discontinued due to AE	0.0	6.2	1.5	4.4
Most Common AEs				
Abnormal dreams	5.1	3.1	6.0	4.4
Dizziness	15.3	63.1	1.5	19.1
Headache	11.9	7.7	14.9	11.8
Diarrhea	6.8	9.2	9.0	8.8
Nausea	1.7	10.8	14.9	11.8
Nasopharyngitis	11.9	7.7	1.5	1.5
Rash	5.1	15.4	6.0	2.9
	White		**Hispanic or Latino**	
	DOR/3TC/TDF N=177	EFV/FTC/TDF N=170	DOR/3TC/TDF N=126	EFV/FTC/TDF N=120
One or more AEs	84.7	91.2	84.9	90.8
Drug-related AEs	29.9	65.9	32.5	59.2
Serious AEs	5.6	6.5	1.6	6.7
Discontinued due to AE	5.6	7.1	0.8	5.8
Most Common AEs				
Abnormal dreams	4.0	17.1	3.2	8.3
Dizziness	6.2	29.4	12.7	38.3
Headache	10.7	9.4	12.7	17.5
Diarrhea	9.6	14.1	14.3	16.7
Nausea	6.2	11.8	6.3	8.3
Nasopharyngitis	11.9	12.4	13.5	7.5
Rash	3.4	13.5	4.8	12.5

*Percent of participants with AE in subgroup (n/N). N = number of participants in subgroup.

Table 4. Clinical Adverse Events (%) by Baseline CD4+ T-cell Count*

	≤200 cells/mm^3		>200 cells/mm^3	
	DOR/3TC/TDF N=44	EFV/FTC/TDF N=46	DOR/3TC/TDF N=320	EFV/FTC/TDF N=318
One or more AEs	88.6	82.6	81.9	91.8
Drug-related AEs	36.4	56.5	30.3	63.8
Serious AEs	4.5	6.5	3.4	5.7
Discontinued due to AE	2.3	6.5	3.1	6.6
Most Common AEs				
Abnormal dreams	4.5	8.7	4.7	11.9
Dizziness	13.6	39.1	8.1	36.8
Headache	6.8	8.7	13.8	12.9
Diarrhea	13.6	8.7	10.3	14.2
Nausea	13.6	6.5	6.9	11.3
Nasopharyngitis	9.1	4.3	10.9	9.1
Rash	9.1	6.5	4.1	12.9

*Percent of participants with AE in subgroup (n/N). N = number of participants in subgroup.

CONCLUSIONS

- In HIV-1 treatment-naïve adults, DOR/3TC/TDF demonstrated virologic and immunologic efficacy comparable to that of EFV/FTC/TDF across baseline clinical characteristics and demographic factors including gender, race/ethnicity, HIV-1 RNA >100,000 copies/mL, and viral subtype
- DOR/3TC/TDF was generally well tolerated, regardless of race, ethnicity, gender, or baseline CD4+ T-cell count
- These findings highlight the consistent efficacy and safety of DOR/3TC/TDF compared with EFV/FTC/TDF

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Acknowledgments

We thank all the patients who participated in this study. The contributions of the investigators and their staff are also gratefully recognized.

Funding for this research was provided by Merck & Co., Inc., Kenilworth NJ, USA.

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