DORAVIRINE IS NON-INFERIOR TO DARUNAVIR+RITONAVIR IN PHASE 3 TREATMENT-NAÏVE TRIAL AT WEEK 48

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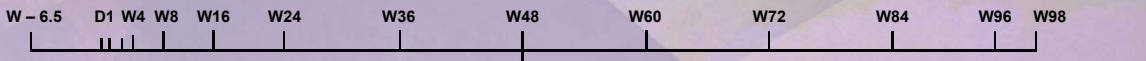
Abstract 45LB

Background

- Doravirine is a novel, next generation 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]
  - Low potential for drug-drug interactions[2]
  - Dosed once daily without regard to food[3]
  - Being developed as a single entity and fixed-dose combination with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC)
- Doravirine 100 mg demonstrated favorable efficacy and a superior neuropsychiatric profile vs efavirenz 600 mg QD in Phase 2b[4]

1. Feng et al, Antimicrob Agents Chemother. 2016 Mar 25;60(4):2241-7., 2. Anderson et al, Antivir Ther. 2015;20(4):397-405., 3. Behm et al ICAAC 2015, Abstract H-778., 4. Gatell et al, J Int AIDS Soc. 2014; 17(4Suppl 3): 19532.

Doravirine vs Darunavir in Treatment-Naive: Design



Key Entry Criteria:

- HIV-1 RNA ≥1000 c/mL within 45 days before Day 1
- Antiretroviral naive
- No genotypic resistance to any study drugs
- Stratification factors: HIV-1 RNA > 100,000 and NRTI choice

Group 1: DOR 100 mg + DRV-PBO + r-PBO + 2 NRTIs — 14 Day Follow-up

Group 2: DOR-PBO + DRV 800 mg + r 100 mg + 2 NRTIs — 14 Day Follow-up

Primary Analysis Time Point

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DOR vs DRV in Treatment-Naïve: Baseline Characteristics

	DOR (N=383)	DRV+r (N=383)
Mean age (SD), years	34.8 (10.5)	35.7 (10.7)
Male	83%	85%
Black/African American	22%	23%
Clinical history of AIDS	9%	10%
HIV-1 subtype B	69%	71%
Baseline HIV-1 RNA		
Mean (SD), $\log_{10}$ copies/mL	4.4 (0.7)	4.4 (0.7)
> 100,000 copies/mL	22%	19%
> 500,000 copies/mL	4%	3%
Baseline CD4+ T-cell Count		
Mean (SD), cells/mm^3	433 (208)	412 (230)
≤ 200 cells/mm^3	11%	17%
NRTIs Selected for Use with Blinded Therapy		
TDF/FTC	87%	88%
ABC/3TC	13%	13%

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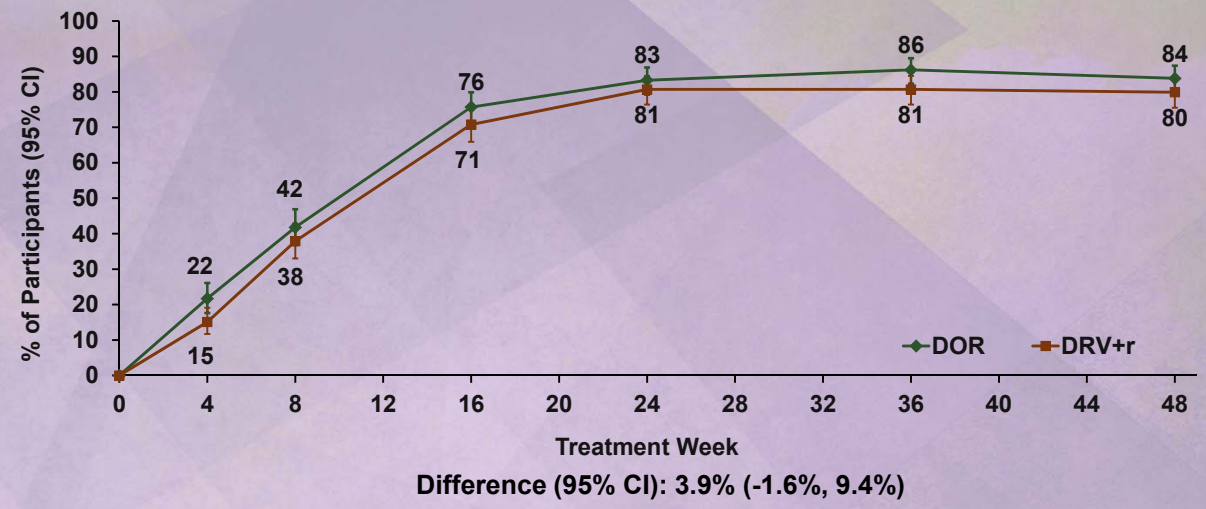
DOR vs DRV in Treatment-Naïve: Efficacy



Difference (95% CI): 3.9% (-1.6%, 9.4%)

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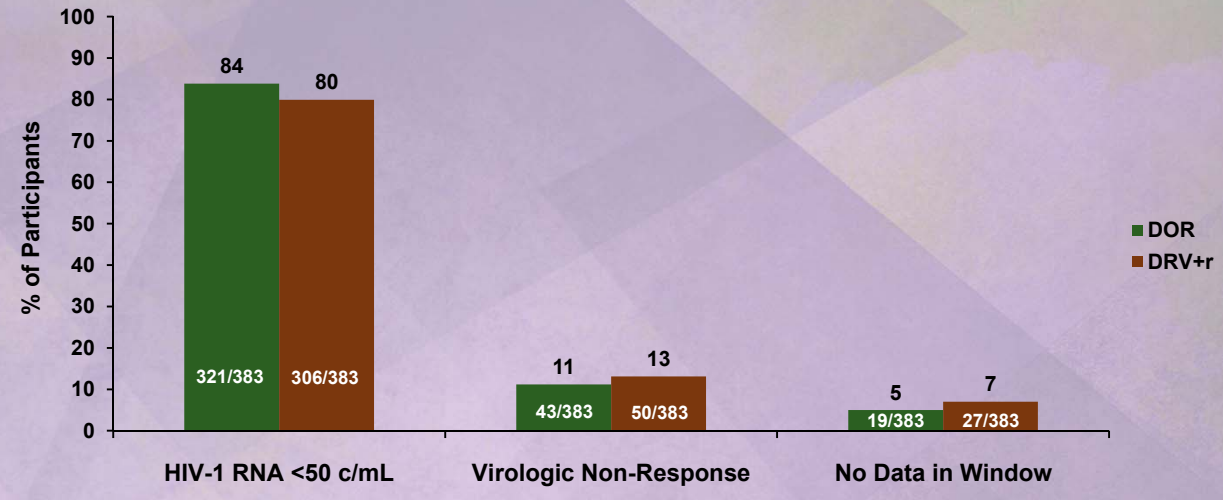
DOR vs DRV in Treatment-Naïve: Results - Virologic Outcome at Week 48, FDA Snapshot Approach



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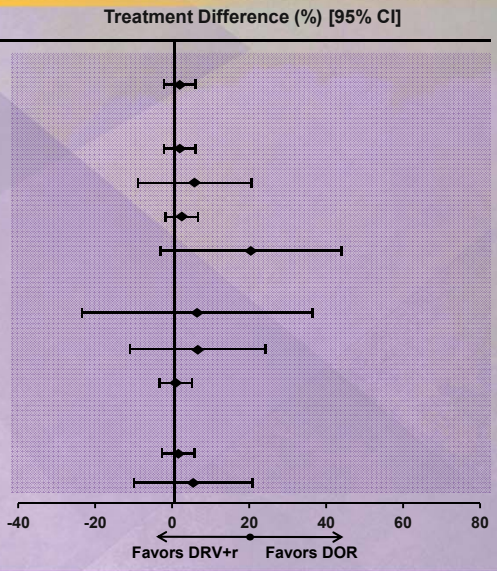
DOR vs DRV in Treatment-Naïve: Results - Subgroups Analysis (Observed Failure)

	HIV-1 RNA <50 c/mL, % (N)	
	DOR	DRV+r
All Participants	88 (364)	86 (355)
Baseline HIV-1 RNA, c/mL		
≤100,000	90 (285)	89 (282)
>100,000	81 (79)	76 (72)
≤500,000	88 (347)	87 (342)
>500,000	82 (17)	50 (12)
Baseline CD4+ T-cell Count, cells/mm^3		
≤50	83 (6)	67 (18)
>50 and ≤200	83 (35)	74 (43)
>200	89 (323)	89 (294)
NRTI Component		
TDF/FTC	88 (316)	87 (312)
ABC/3TC	90 (48)	84 (43)



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DOR vs DRV in Treatment-Naïve: Resistance

- No drug resistance observed in patients with PDVF through Week 48

	DOR (N=383)	DRV+r (N=383)
Patients with PDVF[I], n (%)	19 (5.0%)	24 (6.3%)
Genotype test successfully performed, n	7	8
Primary DOR Resistance	0	0
Primary NRTI resistance	0	0
Primary PI resistance	0	0
Phenotype test successfully performed, n	6	8
With any phenotypic drug resistance	0	0

- One participant discontinued due to noncompliance at Week 24 and developed DOR resistance (RT V106I, and F227C; >90-fold increased IC_{50}) and FTC resistance (RT m184V)
- One participant discontinued due to rash at Week 2 and had DOR IC50 fold change 2.8 from WT (assay resistance cutoff of 2.5), but no genotypic resistance

I Protocol defined virologic failure (PDVF): Confirmed HIV-1 RNA ≥ 50 c/mL after initial response of HIV-1 RNA <50 c/mL; or confirmed HIV-1 RNA ≥ 200 c/mL at Week 24 or Week 36; or confirmed HIV-1 RNA ≥ 50 copies/mL at Week 48.

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DOR vs DRV in Treatment-Naïve: Clinical Adverse Events

	DOR (N=383)		DRV+r (N=383)	
	n	(%)	n	(%)
One or more AE	307	(80%)	300	(78%)
Drug-related AE	117	(31%)	123	(32%)
Serious AE	19	(5%)	23	(6%)
Discontinued due to AE	6	(2%)	12	(3%)
Most Common AE's (≥ 10% in either group)				
Diarrhea	54	(14%)	86	(22%)
Nausea	41	(11%)	46	(12%)
Nasopharyngitis	30	(8%)	39	(10%)
Headache	53	(14%)	41	(11%)
AEs of Clinical Interest				
Rash†	28	(7%)	32	(8%)
Neuropsychiatric‡	44	(11%)	50	(13%)

Superior Lipid Profile for Fasting LDL-C and Non-HDL-C

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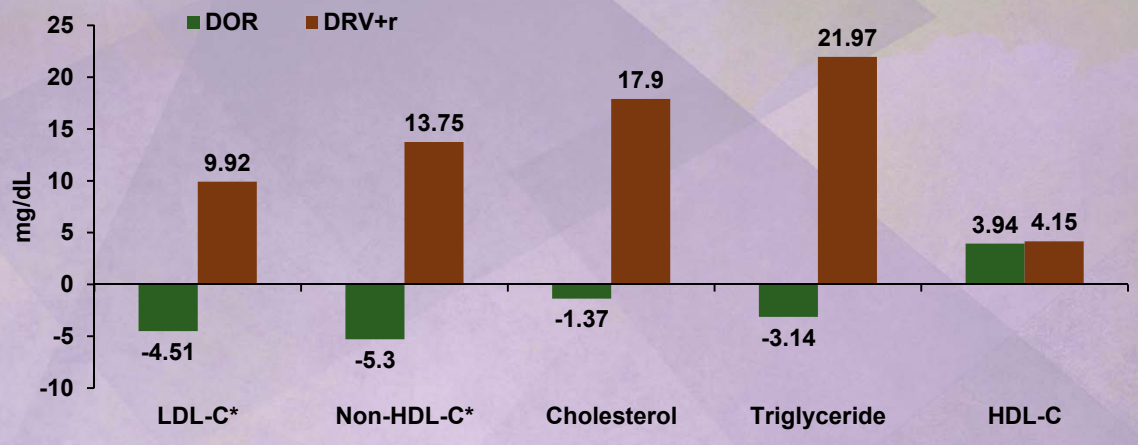
DOR vs DRV in Treatment-Naïve: Fasting Lipids, Change from Baseline at Week 48



* P<0.0001 for DOR vs DRV+r. Statistical testing for other parameters was not prespecified.

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Conclusions

- In HIV-1 infected treatment-naïve participants, doravirine in combination therapy demonstrated:
  - Potency with non-inferior efficacy to darunavir 800 mg + ritonavir 100 mg regardless of baseline HIV-1 RNA
  - Low rate of resistance with only 1/383 participants on doravirine developing genotypic and phenotypic resistance to any study drug through Week 48
- Doravirine was generally well tolerated and safe
  - Superior lipid profile for fasting LDL-C and non-HDL-C compared to darunavir 800 mg + ritonavir 100 mg
  - Low rate of discontinuations due to rash or neuropsychiatric adverse events
- Doravirine is a novel once-daily NNRTI for first-line treatment with consistent efficacy regardless of baseline viral load and very good tolerability

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