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HIV

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Molina J-M, Squires K, Sax PE, et al, for the DRIVE-FORWARD Study Group. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *Lancet HIV* 2018; published online March 25. http://dx.doi.org/10.1016/S2352-3018(18)30021-3.

APPENDIX: SUPPLEMENTARY MATERIAL

TABLE OF CONTENTS

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Participant Exclusion Criteria

1. History or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of the study or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate.

2. Use of recreational or illicit drugs or a recent history of drug or alcohol abuse or dependence. The nature and potential clinical context of the subject's illicit drug use, in relation to their exclusion from this trial, will be at the discretion of the Investigator.

3. Treatment for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1, including but not limited to adefovir, tenofovir, entecavir, emtricitabine, or lamivudine. Note: Subjects may be enrolled if treatment occurred prior to the diagnosis of HIV.

4. Documented or known resistance to any study drug, as defined below:

    a. Resistance to doravirine (for the purpose of this study) includes the following mutations: L100I, K101E, K101P, K103N, K103S, V106A, V106I, V106M, V108I, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, Y188C, Y188H, Y188L, G190A, G190S, H221Y, L234I, P225H, F227C, F227L, F227V, M230L, M230I.

    b. Resistance to darunavir/ritonavir includes any of the following PI mutations: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V.

    c. Resistance to emtricitabine, tenofovir, abacavir and lamivudine includes the following mutations: M184V/I, K65R, M41L, D67N, K70R/E, T69S, L210W, T215Y/F, K219Q/E, L74V, and Y115F.

5. Participation in a study with an investigational compound/device within 30 days prior to signing informed consent.

6. Use of systemic immunosuppressive therapy or immune modulators within 30 days prior to treatment in this study or is anticipated to need them during the course of the study. Note: Short courses of corticosteroids (e.g., as for asthma exacerbation) will be allowed.

7. Requires or is anticipated to require any of the prohibited medications noted in the protocol.

8. Significant hypersensitivity or other contraindication to any of the components of the study drugs.

9. Current (active) diagnosis of acute hepatitis due to any cause. Subjects with chronic hepatitis B and/or C may enter the study as long as they fulfill all entry criteria, have stable liver function tests, and have no significant impairment of hepatic synthetic function (significant impairment is defined as serum albumin <2.8 mg/dL or INR >1.7 in the absence of another explanation for the abnormal laboratory value).

10. Pregnant, breastfeeding, or expecting to conceive at any time during the study.

11. Expecting to donate eggs or sperm at any time during the study.

12. Has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial.

Table A1. Summary of Efficacy Analyses at Week 48

		Unadjusted Data Summary by Treatment Group		Treatment Difference (Doravirine - Darunavir)[‡]	
Parameter	Missing Data Approach[†]	Doravirine n/N (%)	Darunavir-ritonavir n/N (%)	Estimated Difference	95% CI
Primary Endpoint: Proportion with HIV-1 RNA <50 copies/mL					
Primary Analysis (FAS Population)	Snapshot	321/383 (83.8)	306/383 (79.9)	3.9	(-1.6, 9.4)
Sensitivity Analysis (Per Protocol Population)[§]	Snapshot	316/353 (89.5)	298/341 (87.4)	2.1	(-2.7, 6.9)
Supportive Analysis (FAS Population)	OF	321/364 (88.2)	306/355 (86.2)	1.9	(-3.1, 6.8)
Secondary and Exploratory Endpoints (FAS Population)					
Proportion with HIV-1 RNA <40 copies/mL	Snapshot	319/383 (83.3)	303/383 (79.1)	4.2	(-1.4, 9.7)
Proportion with HIV-1 RNA <40 copies/mL	OF	319/364 (87.6)	303/355 (85.4)	2.2	(-2.9, 7.2)
Proportion with HIV-1 RNA <200 copies/mL	Snapshot	328/383 (85.6)	316/383 (82.5)	3.1	(-2.1, 8.4)
Proportion with HIV-1 RNA <200 copies/mL	OF	328/364 (90.1)	316/355 (89.0)	1.1	(-3.5, 5.6)
		Mean (95% CI)	Mean (95% CI)	Difference	95% CI
Change in CD4+ T-cell count (cells per µL)	OF	193 (172, 214)	186 (168, 204)	7.1	(-20.8, 35.0)

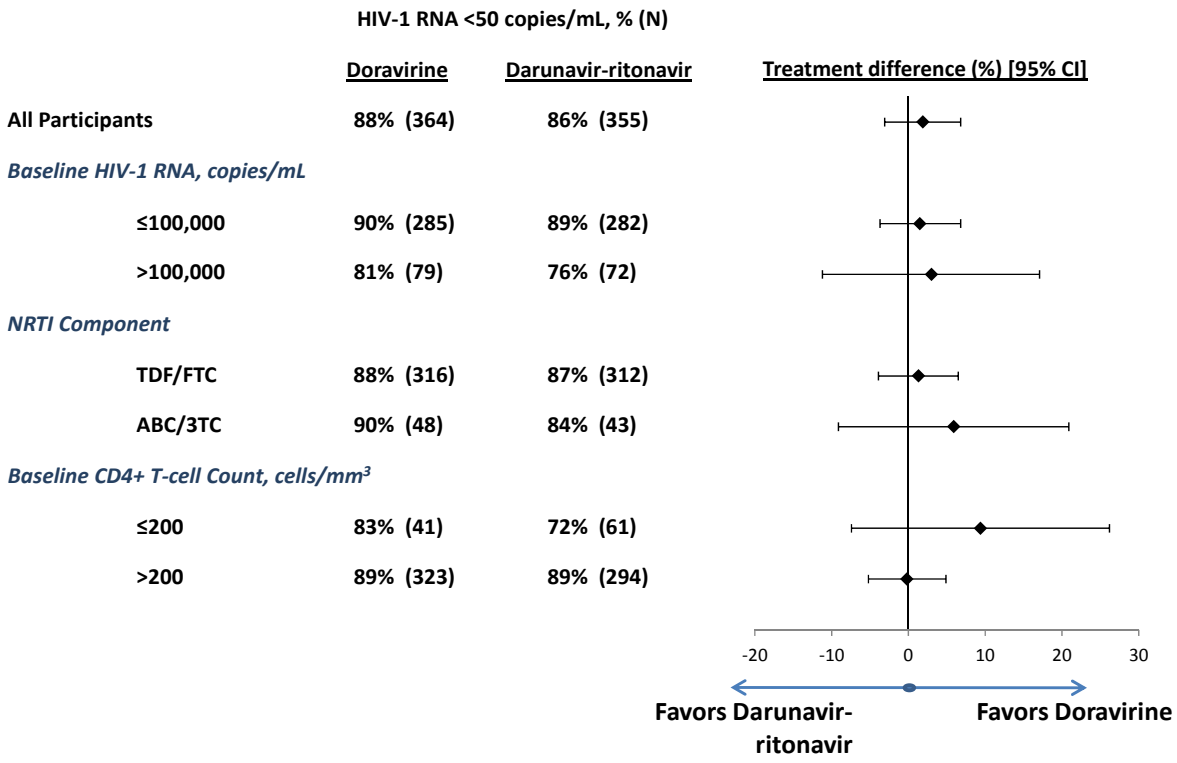
[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum. The 95% CI for mean difference in CD4 change was based on the t-distribution.

[§] The Per-Protocol (PP) population consists of participants in the FAS population with none of the following reasons for exclusion: discontinuation for reasons not related to treatment; major protocol deviations that could affect efficacy; non-compliance with study medication; GCP noncompliance.

Note: Doravirine (100 mg) QD and darunavir/ritonavir (800/100) mg QD were administered with TDF/FTC or ABC/3TC.

Figure A1. Efficacy by Baseline Factors, Observed Failure† Approach



† Discontinuation due to lack of efficacy was counted as failure; data missing for other reasons were excluded. N = number of participants in subgroup.

Table A2. Treatment-Emergent Drug Resistance

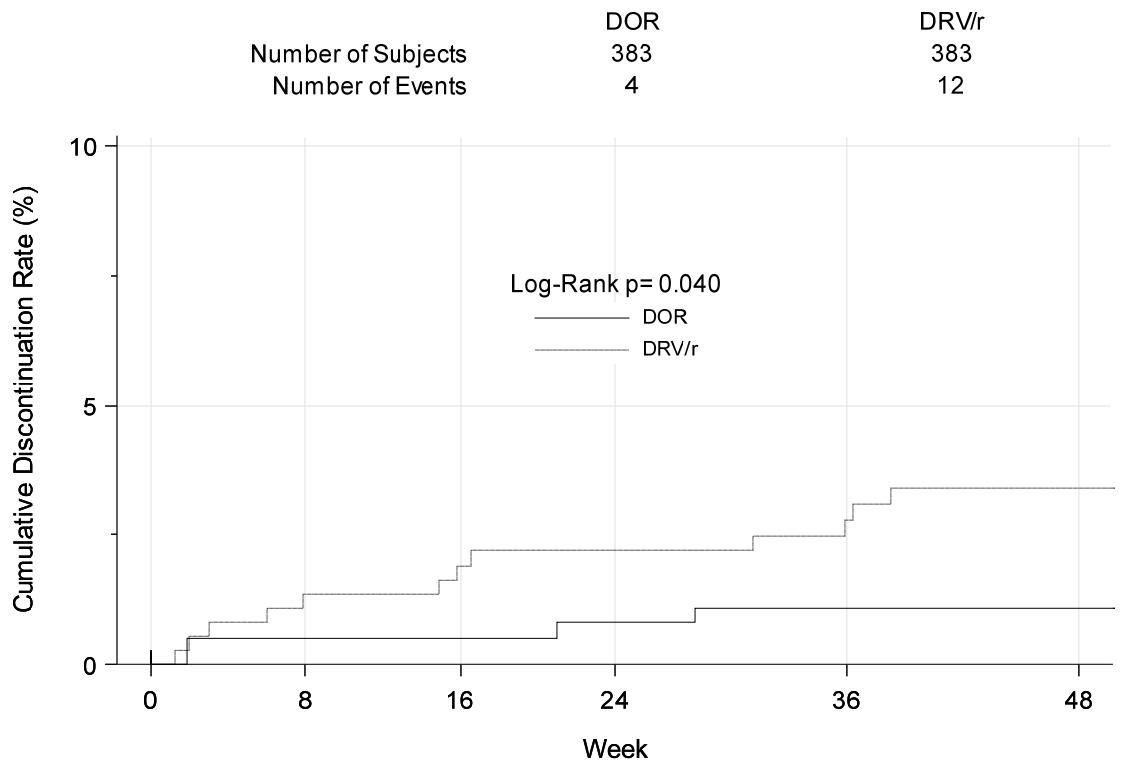
	Doravirine* (N=383) n (%)	Darunavir-ritonavir* (N=383) n (%)
Protocol-defined Virologic Failure[†]	19 (5%)	24 (6%)
Non-response	2 (<1%)	5 (1%)
Rebound	17 (4%)	19 (5%)
Successful genotype test performed	7 (2%)	8 (2%)
Primary NNRTI resistance	0	0
Primary NRTI resistance	0	0
Primary PI resistance	0	0[‡]
Successful phenotype test performed	6 (2%)	8 (2%)
Any phenotypic drug resistance	0	0
Discontinued for reasons other than PDVF	40 (10%)	53 (14%)
Successful genotype test performed	2 (1%)	2 (1%)
Primary NNRTI resistance	1 (<1%)	0
Primary NRTI resistance	1 (<1%)	0
Primary PI resistance	0	0
Successful phenotype test performed	2 (1%)	3 (1%)
Any phenotypic drug resistance	2 (1%)	0

[*] Administered with TDF/FTC or ABC/3TC.

[†] Virologic failure is defined as (1) Non-response: confirmed HIV-1 RNA ≥200 c/mL at week 24 or week 36, or confirmed HIV-1 RNA ≥50 c/mL at week 48; OR (2) Rebound: confirmed HIV-1 RNA ≥ 50 c/mL after initial response of HIV-1 RNA <50 c/mL.

[‡] Polymorphic mutations in the viral protease gene were identified in three participants in the darunavir group but were not associated with decreased phenotypic susceptibility to darunavir.

Figure A2. Time to Discontinuation due to an Adverse Event, Weeks 0-48



Number of subjects at risk

DOR	383	366	356	353	339	303
DRV/r	383	357	349	338	326	287

Table A3. Most Common† Laboratory Abnormalities, DAIDS Grade 3 or 4

Criterion‡	Doravirine		Darunavir-ritonavir		Difference
	n/m	(%)	n/m	(%)	% (95% CI§)
Fasting LDL Cholesterol (mg/dL)					
Grade 3: >=190	1/332	(<1%)	9/320	(3%)	-2.5 (-5.0, -0.8)
Fasting Glucose (mg/dL)					
Grade 3: >250 - 500	4/335	(1%)	1/327	(<1%)	0.9 (-0.6, 2.8)
Creatinine (mg/dL)					
Grade 3: >1.8 - <3.5 x ULN or 1.5 - <2.0 x baseline	5/380	(1%)	10/378	(3%)	-1.3 (-3.6, 0.7)
Aspartate Aminotransferase (IU/L)					
Grade 3: 5.0 - <10.0 x ULN	2/380	(1%)	6/378	(2%)	-1.1 (-3.0, 0.5)
Alanine Aminotransferase (IU/L)					
Grade 3: 5.0 - <10.0 x ULN	4/369	(1%)	6/375	(2%)	-0.5 (-2.5, 1.3)
Lipase (IU/L)					
Grade 3: 3.0 - <5.0 x ULN	6/380	(2%)	6/378	(2%)	-0.0 (-2.0, 2.0)
Grade 4: >=5.0 x ULN	4/380	(1%)	3/378	(1%)	0.3 (-1.4, 2.0)
Creatine Kinase (IU/L)					
Grade 3: 10.0 - <20.0 x ULN	7/380	(2%)	7/378	(2%)	-0.0 (-2.2, 2.1)
Grade 4: >= 20.0 x ULN	6/380	(2%)	7/378	(2%)	-0.3 (-2.4, 1.8)

† Occurring in at least 4 participants in either treatment group.

‡ Participants are counted once per test in the highest grade reported. Only participants with a worsened grade from baseline were included.

§ The 95% CIs were calculated using Miettinen and Nurminen method.

n = Participants with results that met criterion; m = participants with at least one post-baseline test.

ULN = Upper limit of normal range.

Figure A3. Change from Baseline in Serum Creatinine (mg/dL) Over Time