Age, Gender, and Race Analyses of D/C/F/TAF in HIV-1 Treatment-naïve Patients

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INTRODUCTION

- The oral, once-daily, single-tablet regimen darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg is approved in Europe[1] and under regulatory review in the United States for the treatment of human immunodeficiency virus (HIV)–1 infection[2]
- Studies of darunavir (DRV) have demonstrated a durable virologic response, long-term safety, and high barrier to the development of resistance.[3,4] The tenofovir prodrug TAF has shown similar efficacy and improved renal and bone safety compared with tenofovir disoproxil fumarate (TDF)[2,5,6]
- D/C/F/TAF has been evaluated in pivotal phase 3 trials of both treatment-experienced, virologically suppressed (EMERALD) and treatment-naïve (AMBER) patients.[7,8] The AMBER trial demonstrated that D/C/F/TAF was noninferior to use of D/C + F/TDF at Week 48[8]

OBJECTIVE

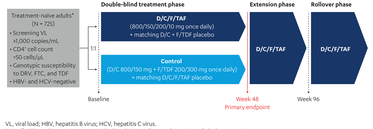
- To evaluate Week 48 efficacy and safety results from the AMBER trial of treatment-naïve patients receiving D/C/F/TAF across subgroups based on age, gender, and race

METHODS

Study Design

- Treatment-naïve adults with HIV-1 infection were enrolled in the ongoing phase 3, randomized, noninferiority AMBER trial (**Figure 1**)[8]
  - Patients with baseline resistance-associated mutations (RAMs; except to DRV, emtricitabine [FTC], or TDF) were eligible

Figure 1. AMBER study design.



VL, viral load; HBV, hepatitis B virus; HCV, hepatitis C virus.
*Stratified by VL (≤ or >100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/μL) at screening.

Analyses

- The primary endpoint in AMBER was the proportion of patients with virologic response at Week 48
  - Virologic response was defined as VL <50 copies/mL (US Food and Drug Administration [FDA] snapshot)
  - For virologic response rates, the difference (95% confidence interval [CI]) between the D/C/F/TAF and control groups was calculated as follows:
    - Overall population: stratum-adjusted Mantel-Haenszel test with stratification factors of VL (≤ or >100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/μL)
    - Subgroups: exact CIs
- Safety assessments included adverse event (AE) reports and changes in bone mineral density (BMD) and estimated glomerular filtration rate (eGFR) from baseline to Week 48 (calculated using serum cystatin C [Chronic Kidney Epidemiology Collaboration formula]; $eGFR_{cystC}$)
- Analyses were performed using all randomized patients who received ≥1 dose of study drug (intention-to-treat population)
- Results were evaluated in subgroups based on age (≤50 vs >50 years), gender, and race (black/African American vs non-black/African American)
  - Analysis of race subgroups excluded patients with race categorized as "unknown" or "not reported"

RESULTS

Patient Population

- Baseline demographic and HIV-1 disease characteristics were balanced between the D/C/F/TAF and control arms overall (**Table 1**)

Table 1. Baseline Demographic and Clinical Characteristics (Overall Population)

Parameter	D/C/F/TAF (N = 362)	Control (N = 363)
Demographic characteristics		
Median age (range), y	34 (19-61)	34 (18-71)
Age category, n (%)		
≤50 y	326 (90)	331 (91)
>50 y	36 (10)	32 (9)
Gender, n (%)		
Men	318 (88)	322 (89)
Women	44 (12)	41 (11)
Race, n (%)*		
Non-black/African American	305 (88)	309 (89)
Black/African American	40 (12)	40 (11)
Clinical characteristics		
Time since diagnosis, median (range), mo	5.7 (0.6-194.3)	4.3 (0.7-310.3)
Log_{10} VL, median (range), copies/mL†	4.4 (1.3-6.6)	4.6 (3.0-6.7)
CD4+ cell count, median (range), cells/μL*	462 (46-1,454)	440 (38-1,456)

*Percentages calculated excluding patients with "unknown" or "not reported" race.
†VL and CD4+ cell count data at baseline.

Efficacy

- Virologic response rates with D/C/F/TAF and control were similar overall and across age, gender, and race subgroups (**Figure 2**)

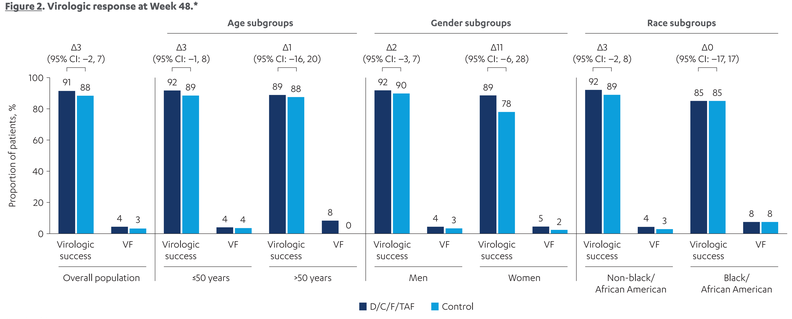
Resistance

- Among the 9 patients with available data, none developed post-baseline DRV or primary protease inhibitor (PI) RAMs[8]
- One patient (D/C/F/TAF group) developed M184I/V, an FTC and lamivudine RAM. This patient had K103N at screening, indicating transmitted nonnucleoside reverse transcriptase inhibitor (efavirenz/nevirapine) resistance[8]

Safety

- Overall, AE rates were similar in the D/C/F/TAF and control arms, and no clinically relevant differences were observed across subgroups (**Table 2**)
- The most common study drug–related AEs overall (≥5% of patients in either arm) were diarrhea (D/C/F/TAF, n = 31 [9%]; control, n = 40 [11%]), rash (n = 22 [6%]; n = 14 [4%]), and nausea (n = 20 [6%]; n = 36 [10%])
- Overall, there was 1 clinical renal AE of interest (D/C/F/TAF arm); there were no clinical renal AEs of interest that were considered related to study drug in any subgroup
- Improvements in $eGFR_{cystC}$ were observed with D/C/F/TAF versus control overall,[8] and the results were generally consistent across subgroups (**Figure 3A-C**)
- Lower rates of bone AEs of interest and increases in BMD were observed with D/C/F/TAF versus control overall and across subgroups (**Table 3** and **Figure 3D-F**)[8]

Figure 2. Virologic response at Week 48.*



VF, virologic failure.
*Overall, 15 (4%) patients treated with D/C/F/TAF and 30 (8%) patients treated with control did not have virologic response data at Week 48. For each subgroup, patients with missing data in the D/C/F/TAF and control treatment groups, respectively, were as follows: 4% and 8% of those aged ≤50 years, 3% and 13% aged >50 years, 4% and 7% men, 7% and 20% women, 4% and 8% non-black/African American, and 8% and 8% black/African American.

Table 2. Incidence (%) of AEs Through Week 48

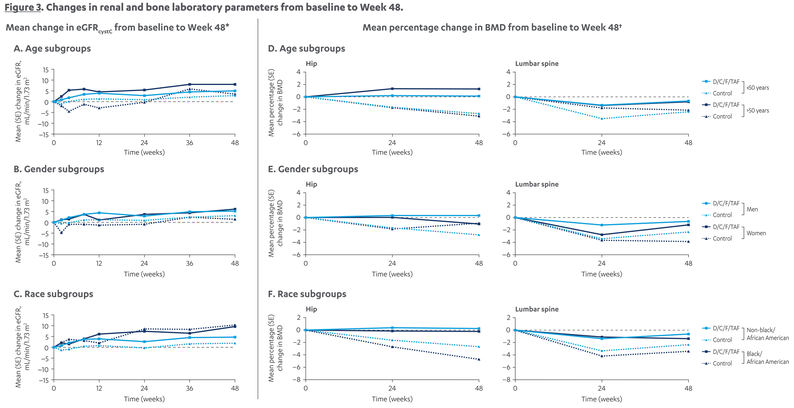
			Age subgroups				Gender subgroups				Race subgroups			
	Overall population		≤50 years		>50 years		Men		Women		Non-black/ African American		Black/ African American	
Parameter, %	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control
n	362	363	326	331	36	32	318	322	44	41	305	309	40	40
≥1 AE*	86	85	85	85	94	81	86	85	91	85	85	86	88	68
Discontinued due to an AE	2	4	2	4	0	9	2	3	5	12	2	5	0	0
≥1 grade 3-4 AE	5	6	4	6	17	9	5	6	9	10	5	7	5	3
≥1 serious AE	5	6	4	5	11	9	4	5	7	10	5	7	5	3

*There were no deaths in any group.

Table 3. Incidence (%) of Bone AEs of Interest Through Week 48

			Age subgroups				Gender subgroups				Race subgroups			
	Overall population		≤50 years		>50 years		Men		Women		Non-black/ African American		Black/ African American	
Parameter, %	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control
n	362	363	326	331	36	32	318	322	44	41	305	309	40	40
Bone loss/atrophy	6	10	6	10	8	9	7	11	2	2	7	12	0	0
Related	1	3	1	3	0	0	1	3	0	0	1	3	0	0
Fracture, other	1	1	1	1	3	0	1	<1	2	2	1	1	0	0
Related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fracture, possibly osteoporotic	<1	0	<1	0	0	0	<1	0	0	0	<1	0	0	0
Related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other bone events	1	0	<1	0	3	0	1	0	0	0	1	0	0	0
Related	<1	0	<1	0	0	0	<1	0	0	0	<1	0	0	0

Figure 3. Changes in renal and bone laboratory parameters from baseline to Week 48.



SE, standard error.
*Measured at Weeks 0, 2, 4, 8, 12, 24, 36, and 48.
†Data are from the bone investigation substudy, which included 113 patients in the D/C/F/TAF arm and 99 patients in the control arm.

CONCLUSIONS

- **Efficacy and safety results for D/C/F/TAF versus control were consistent across subgroups by age, gender, and race through Week 48 in treatment-naïve patients with HIV-1 infection**
  - **The analyses were limited by the small numbers of patients in the subgroups (eg, >50 years, women, black/ African American)**
- **D/C/F/TAF achieved a high virologic response rate of 91.4%, which was noninferior to control (88.4%)**
- **VF rates were low, and development of primary PI or DRV RAMs was not observed upon VF**
- **Favorable renal and bone outcomes were observed with D/C/F/TAF relative to control**

REFERENCES

1. SYMTUZA (darunavir/cobicistat/emtricitabine/tenofovir alafenamide) [summary of product characteristics]. Beerse, Belgium: Janssen-Cilag NV; October 2017.
2. Mills A, et al. *J Acquir Immune Defic Syndr*. 2015;69(4):439-445.
3. Lathouwers E, et al. *HIV Clin Trials*. 2017;18(5-6):196-204.
4. Orkin C, et al. *HIV Med*. 2013;14(1):49-59.
5. Ruane PJ, et al. *J Acquir Immune Defic Syndr*. 2013;63(4):449-455.
6. De Clercq E. *Biochem Pharmacol*. 2016;119:1-7.
7. Orkin C, et al. *Lancet HIV*. 2018;5(1):e23-e34.
8. Gallant J, et al. Presented at: European AIDS Conference; October 25-27, 2017; Milan, Italy. Oral presentation PS8/2.

DISCLOSURES

B. Rashbaum, C. McDonald, C. Mussini, and C.D. Spinner contributed to the conduct of the study as investigators and to the interpretation of the data. J. Jezorwski contributed to statistical analysis and interpretation of the data. E.Y. Wong and K. Brown contributed to the design of the study and interpretation of the data. All authors contributed to drafting the poster and approved the final version.

B. Rashbaum has participated in speakers bureaus for Gilead and Johnson & Johnson and is a stockholder for Gilead. C. McDonald reports personal fees from Gilead, Merck, ViiV, and Janssen. C. Mussini and C.D. Spinner report no conflicts of interest. J. Jezorwski, E.Y. Wong, and K. Brown are full-time employees of Janssen.

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