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Week 96 efficacy and safety results of the phase 3, randomized EMERALD trial to evaluate switching from boosted-protease inhibitors plus emtricitabine/tenofovir disoproxil fumarate regimens to the once daily, single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in treatment-experienced, virologically-suppressed adults living with HIV-1

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ABSTRACT

Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg was investigated through 96 weeks in EMERALD (NCT02269917).

Virologically-suppressed, HIV-1-positive treatment-experienced adults (previous non-darunavir virologic failure [VF] allowed) were randomized (2:1) to D/C/F/TAF or boosted protease inhibitor (PI) plus emtricitabine/tenofovir-disoproxil-fumarate (F/TDF) over 48 weeks. At week 52 participants in the boosted PI arm were offered switch to D/C/F/TAF (late-switch, 44 weeks D/C/F/TAF exposure). All participants were followed on D/C/F/TAF until week 96. Efficacy endpoints were percentage cumulative protocol-defined virologic rebound (PDVR; confirmed viral load [VL] $\geq$50 copies/mL) and VL $<$ 50 copies/mL (virologic suppression) and $\geq$50 copies/mL (VF) (FDA-snapshot analysis).

Of 1141 randomized patients, 1080 continued in the extension phase. Few patients had PDVR (D/C/F/TAF: 3.1%, 24/763 cumulative through week 96; late-switch: 2.3%, 8/352 week 52–96). Week 96 virologic suppression was 90.7% (692/763) (D/C/F/TAF) and 93.8% (330/352) (late-switch). VF was 1.2% and 1.7%, respectively. No darunavir, primary PI, tenofovir or emtricitabine resistance-associated mutations were observed post-baseline. No patients discontinued for efficacy-related reasons. Few discontinued due to adverse events (2% D/C/F/TAF arm). Improved renal and bone parameters were maintained in the D/C/F/TAF arm and observed in the late-switch arm, with small increases in total cholesterol/high-density-lipoprotein-cholesterol ratio. A study limitation was the lack of a control arm in the week 96 analysis.

Through 96 weeks, D/C/F/TAF resulted in low PDVR rates, high virologic suppression rates, very few VFs, and no resistance development. Late-switch results were consistent with D/C/F/TAF week 48 results. EMERALD week 96 results confirm the efficacy, high genetic barrier to resistance and safety benefits of D/C/F/TAF.

1. Introduction

For long-term virologic success in the treatment of HIV-1 infection, sustained efficacy, long-term safety, tolerability, a high genetic barrier to resistance and convenience are important considerations, given the prolonged time individuals will receive antiretroviral treatment (ART). Since the approval of boosted darunavir (DRV) in 2006, a wealth of clinical trial data and clinical experience has been generated, which demonstrates its high, durable virologic response, high genetic barrier to resistance, and long-term safety in a broad range of patients (Cahn et al., 2011; Eron et al., 2018; Flynn et al., 2014; Lathouwers et al., 2017; Orkin et al., 2013, 2018).

Once-daily, single-tablet HIV-1 treatment regimens (STRs) are preferred by patients and improve treatment adherence and satisfaction, potentially reducing the rate of virologic failure (VF) and emergence of antiretroviral resistance, resulting in a higher probability of long-term viral load (VL) suppression, compared with multi-tablet regimens (Clay et al., 2015; Nachega et al., 2011; Sterrantino et al., 2012). A once-daily, STR combining darunavir with cobicistat, emtricitabine, and tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg, was recently approved in the US, EU, and Canada (SYMTUZA™ tablets Summary of Product Characteristics, 2017; Prescribing information for SYMTUZA™, 2018).

The primary 48-week analyses of the phase 3 AMBER (NCT02431247) (Eron et al., 2018) and EMERALD (NCT02269917) (Orkin et al., 2018) trials showed that D/C/F/TAF had high, non-inferior antiviral efficacy with more favorable renal and bone safety versus D/C plus emtricitabine/tenofovir disoproxil fumarate (F/TDF) in ART-naïve adults in AMBER (Eron et al., 2018) and versus boosted protease inhibitor (bPI) plus F/TDF in ART-experienced, virologically suppressed adults in EMERALD (Orkin et al., 2018).

Treatment guidelines include the D/C/F/TAF STR or DRV boosted with ritonavir or cobicistat combined with 2 nucleoside or nucleotide analogs reverse transcriptase inhibitors (N(t)RTIs) as a recommended treatment option (EACS, 2018) or recommend in certain clinical situations, such as for those patients who may have uncertain adherence, those who require a regimen with a high genetic barrier to resistance, or those patients who may not have resistance results available (Panel on Antiretroviral Guidelines for Adults and Adolescents, updated July 10, 2019; Saag et al., 2018).

A predefined week 96 analysis of the efficacy and safety of D/C/F/TAF in the EMERALD clinical trial is presented.

Abbreviations

AE	adverse event
ART	antiretroviral treatment
BMD	bone mineral density
bPI	boosted protease inhibitor
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DRV	darunavir
F/TDF	emtricitabine/tenofovir-disoproxil-fumarate
N(t)RTI	nucleoside(tide) analog reverse transcriptase inhibitor
PDVR	protocol-defined virologic rebound
PI	protease inhibitor
RAM	resistance-associated mutation
STR	single-tablet HIV-1 treatment regimen
VF	virologic failure
VL	viral load

2. Material and methods

2.1. Study design and patients

Detailed methods for EMERALD (TMC114IFD3013) have been previously reported (Orkin et al., 2018). Briefly, EMERALD is a phase 3, randomized, active-controlled, open-label, non-inferiority study conducted at 106 sites across 9 countries. The study included ART-experienced, HIV-1-positive adults who were virologically suppressed (VL < 50 copies/mL for ≥ 2 months before screening; one VL 50–200 copies/mL within 12 months prior to screening was allowed) on stable bPI (DRV/ritonavir or DRV/cobicistat once daily, atazanavir/ritonavir or atazanavir/cobicistat once daily, or lopinavir/ritonavir twice daily) plus F/TDF regimens for ≥ 6 months. Previous non-DRV VF was allowed. If historical genotypes were available, absence of DRV resistance-associated mutations (RAMs) was required in line with the DRV once daily indication.

The trial consisted of a 48-week treatment period during which patients were randomized (2:1) to switch to the once daily D/C/F/TAF 800/150/200/10 mg STR or continue on a bPI combined with F/TDF. Patients could then continue on D/C/F/TAF (D/C/F/TAF arm) or switch from bPI plus F/TDF to D/C/F/TAF at week 52 (late switch arm, 44 weeks of D/C/F/TAF exposure) in an extension phase until week 96, with study visits every 12 weeks. After week 96 participants were given the opportunity to remain in the trial until the study drug became commercially available.

2.2. Study endpoints

The primary endpoint was protocol-defined virologic rebound (PDVR), defined as the proportion of patients with confirmed VL ≥ 50 copies/mL or premature discontinuations irrespective of reason with last VL ≥ 50 copies/mL, cumulative through week 48 in each arm. Secondary efficacy endpoints were cumulative PDVR from baseline through week 96 in the D/C/F/TAF arm and cumulative PDVR from week 52 through week 96 in the late switch arm, and virologic outcome at week 96 (VL < 50 and ≥ 50 copies/mL [VF]; FDA-snapshot analysis) in all randomized participants in the D/C/F/TAF arm and based on only those who switched in the boosted PI arm, comprising 44 weeks of D/C/F/TAF exposure. Efficacy endpoints were also evaluated at the 200 copies/mL cutoff.

Other secondary endpoints included change in $CD4^+$ cell count, post-baseline HIV-1 genotypic resistance (GenoSure MG) in PDVRs with VL ≥ 400 copies/mL at failure (preferably at confirmed rebound), at later post-rebound time points or at discontinuation, adherence to treatment based on drug accountability, adverse event (AE) incidences, changes in serum creatinine, estimated glomerular filtration rate based on serum creatinine ($eGFR_{cr}$, Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] [Laterza et al., 2002]) and eGFR based on cystatin C ($eGFR_{cyst}$, CKD-EPI formula [Laterza et al., 2002; Levey et al., 2009]), and ratios of total urine protein, urine albumin, retinol binding protein, and β-2-microglobulin to creatinine (UPCR, UACR, RPB:Cr and B2M:Cr, respectively). Retrospectively, HIV-1 proviral DNA was sequenced from baseline samples (VL < 50 copies/mL) to assess the

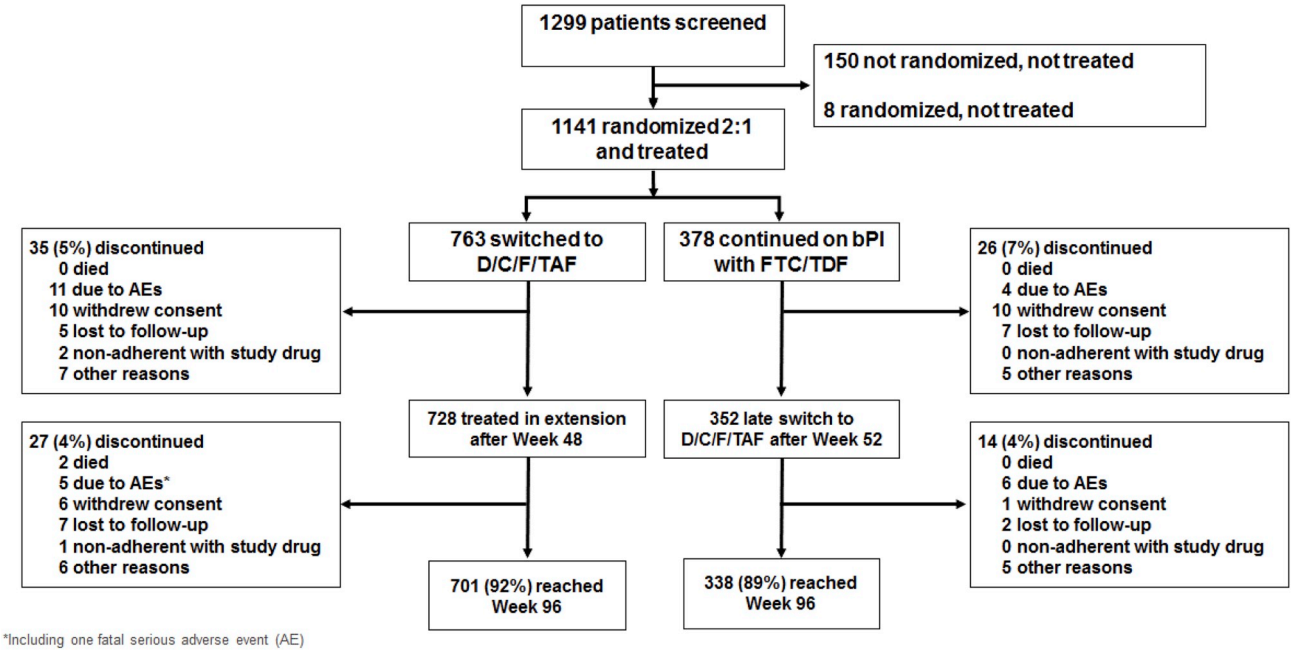

Fig. 1. Patient disposition for EMERALD through 96 weeks.

prevalence of archived RAMs in patients with prior VF.

Endpoints in the bone investigation substudy were percentage change in hip, lumbar spine, and femoral neck bone mineral density (BMD) measured by DXA scans, changes in associated T-score (normal BMD defined as a T-score ≥ -1; osteopenia as a T-score from ≥ -2.5 to < -1; and osteoporosis as a T-score < -2.5), and changes in bone biomarkers.

2.3. Statistical analysis

The main outcome analysis for the D/C/F/TAF arm was based on the intent-to-treat population, which included all randomized patients who received at least 1 dose of study drug. For the control arm, the week 96 analysis was based on patients who switched at week 52. A per-protocol analysis was also performed, which excluded patients with major protocol violations or other predefined criteria that potentially affected the efficacy outcome (Supplementary Table 1).

Data analysis was performed using SAS software (SAS Institute, Inc, Cary, NC, USA) version 9.2. Least squares mean change from reference in $CD4^+$ cell count (non-completer equaled failure; last observation was carried forward otherwise) and associated 95% confidence intervals (CIs) were evaluated with ANCOVA, including a term for bPI used at screening and reference $CD4^+$ count value as a covariate, fit separately for each treatment arm. Within treatment arm comparisons for change at week 96 from reference were assessed by Wilcoxon signed-rank test for eGFR, renal biomarkers and fasting lipids and by paired *t*-test for BMD. Reference for the D/C/F/TAF arm was baseline. Reference for the late switch arm was the last value before the switch.

3. Results

3.1. Patient baseline characteristics and disposition

Overall (N = 1141) demographic and disease characteristics at baseline have been previously described (Orkin et al., 2018) (Supplementary Table 2). Median age was 46 years and most were male (82%), white (75%), and receiving boosted DRV (70%) at screening. Median (IQR) time since HIV diagnosis was 9.3 (4.2–18.1) years. Overall, previous ART (including screening ART and PI booster counted as a separate antiretroviral) included: ≥8 antiretrovirals (27% [312/1141]); ≥5 antiretrovirals (58%), ≥2 PIs (41%), ≥3 N(t)RTIs (42%), ≥1 non-nucleoside reverse transcriptase inhibitor (NNRTI) (30%), and ≥1 integrase inhibitor (6%). Overall, 169 (15%) patients had previous antiretroviral VF (7% on a PI, 11% on an N(t)RTI, 6% on an NNRTI, and 1% on an integrase inhibitor).

Of 1141 patients randomized and treated, 1087/1141 patients (95%) completed 48 weeks, and 1080 patients (95%) continued in the extension phase (N = 728 D/C/F/TAF [95%]; N = 352 late switch [93%]) with 1036 patients (91%) ongoing on study treatment through 96 weeks (Fig. 1). From week 48 through 96 weeks, the most common reasons for discontinuation, as indicated by the investigator, were AEs, loss to follow-up and withdrawn consent (Fig. 1) with a similar

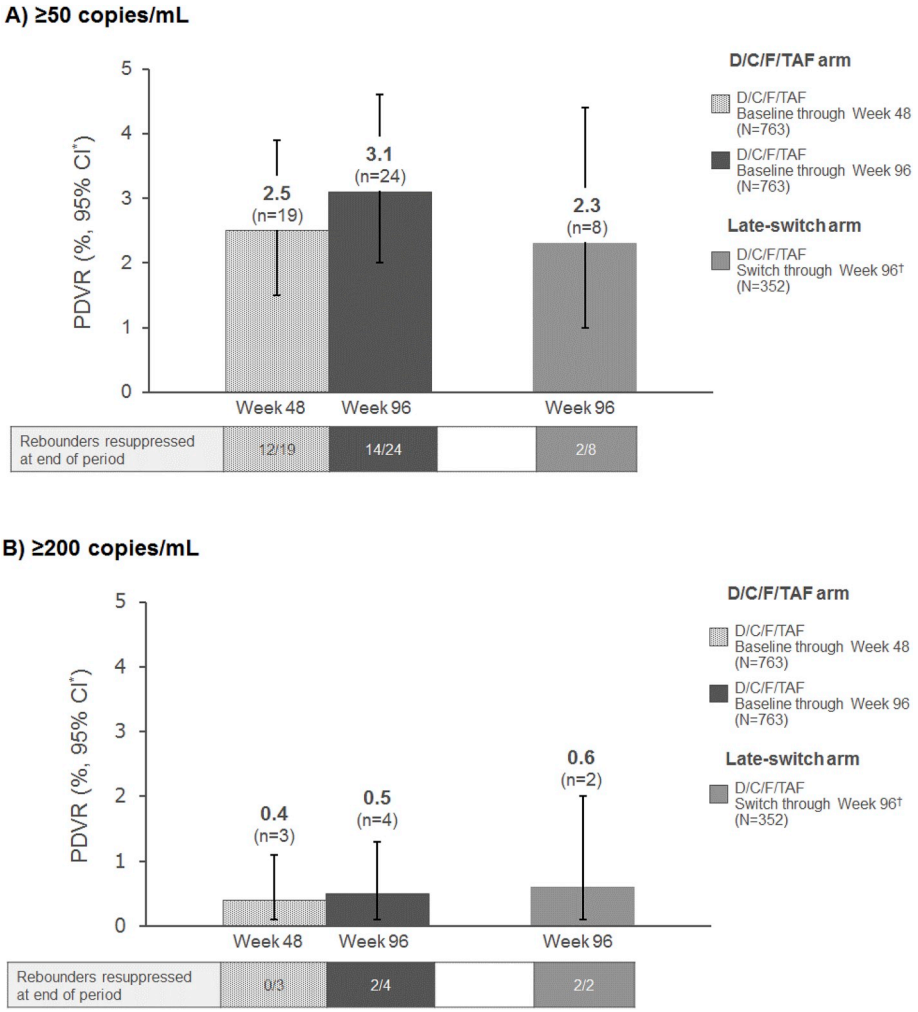

Fig. 2. Protocol-defined virologic rebound (PDVR) through Week 96; A) ≥50 copies/mL and B) ≥200 copies/mL.
*Two-sided Exact Clopper-Pearson 95% confidence interval (CI); †Comprising 44 weeks of D/C/F/TAF exposure.

proportion between arms (4%).

3.2. Efficacy analyses

Few patients had PDVR (VL ≥ 50 copies/mL) cumulative through week 96 in the D/C/F/TAF arm (3.1%, 24/763) (Fig. 2A). In the late switch arm, PDVR occurred in 2.3% of patients (8/352) from week 52 through week 96 (Fig. 2A). Of the patients with PDVR, 14/24 in the D/C/F/TAF arm through week 96 and 2/8 in the late switch arm from week 52 through week 96 resuppressed by week 96 while maintaining D/C/F/TAF therapy (Fig. 2A). There were 4/763 (0.5%) PDVRs (VL ≥ 200 copies/mL) in the D/C/F/TAF arm cumulative through week 96 and 2/352 (0.6%) over 44 weeks in the late switch arm (Fig. 2B). PDVR (VL ≥ 50 copies/mL) cumulative through week 96 was consistent using the per-protocol analysis (Supplementary Table 3). Through 96 weeks, no patient in the D/C/F/TAF arm discontinued dosing due to loss of virologic efficacy.

At week 96, VL ≥ 50 copies/mL (FDA-snapshot analysis) occurred in 9/763 (1.2%) patients in the D/C/F/TAF arm and in 6/352 (1.7%) patients in the late switch arm (Fig. 3A and Supplementary Table 4). A high proportion of patients in the D/C/F/TAF arm (90.7%, 692/763) and late switch arm (93.8%, 330/352) had a VL < 50 copies/mL (FDA-snapshot analysis) at week 96 (Fig. 3A and Supplementary Table 4). Of those who were < 50 copies/mL at week 48, 95.2% (689/724) (D/C/F/TAF arm) and 93.7% (328/350) (late switch arm) maintained virologic suppression at week 96. Virologic responses were consistent with the FDA-snapshot analysis using the VL < 200 copies/mL cutoff (Fig. 3B and Supplementary Table 4) and the per-protocol < 50 copies/mL FDA-snapshot analysis (Supplementary Table 3).

PDVR and FDA-snapshot outcomes were consistent across the baseline patient subgroups, sex, age, race, previous antiretroviral use, and previous antiretroviral VF (Supplementary Table 5). In the D/C/F/TAF arm, of the 116 patients with ≥1 previous antiretroviral VF, PDVR occurred in 4.3% of patients (5/116) and 87.1% (101/116) were suppressed (VL < 50 copies/mL; FDA-snapshot analysis) at week 96.

3.3. Immunologic response

The least squares mean (95% CI) increase from baseline in $CD4^+$ cell count to week 96 was 32.1 (95% CI: 16.4 to 47.8) cells/mm^3 in the D/C/F/TAF arm. In the late switch arm, the increase from the last value prior to switch to week 96 was 13.1 (95% CI: -8.0 to 34.1) cells/mm^3.

3.4. Resistance analysis

Few patients had PDVR cumulative through 96 weeks, with most having low VL values throughout the study, so very few samples were eligible for genotyping (HIV-1 RNA ≥ 400 copies/mL at rebound or at later time points). Through week 96, 4 out of 24 rebounders in the D/C/F/TAF arm had post-baseline genotype data, and 2 out of 8 rebounders in the late switch arm had genotype data after week 52. No DRV, primary PI, tenofovir or emtricitabine RAMs (Wensing et al., 2014) were observed post baseline. All patients had HIV-1 virus susceptible to all drugs in the regimens. One patient in the D/C/F/TAF arm had a secondary PI RAM L63P and an NNRTI RAM K103N, conferring resistance to efavirenz (EFV) and nevirapine, which was probably related to previous virologic failure of EFV/F/TDF and previous use of nevirapine.

3.5. Adherence to treatment

Median (IQR) cumulative adherence to the end of week 96, as measured by pill count, was 99.7% (98.2%; 100.2%) in patients in the D/C/F/TAF arm. Median (IQR) cumulative adherence was 99.2% (96.9%; 100.0%) from baseline to week 52 and 99.7% (97.4%, 100.0%) from week 52 to week 96 in the late switch arm.

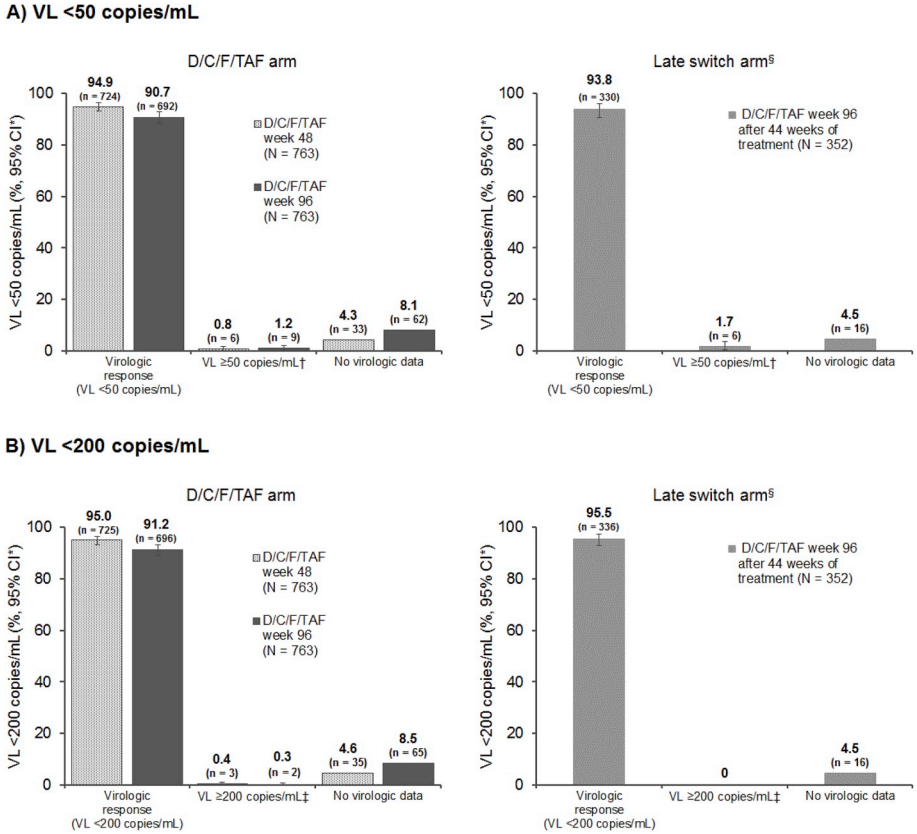

Fig. 3. FDA-snapshot analysis at weeks 48 and 96; A) < 50 copies/mL and B) < 200 copies/mL.
*Two-sided Exact Clopper-Pearson 95% confidence interval (CI); †Last VL in week 48 or week 96 window ≥ 50 copies/mL, or discontinuation for efficacy reasons, or premature discontinuations (not due to efficacy, adverse events or death), with last (single) VL ≥ 50 copies/mL; ‡Last VL in week 48 or week 96 window ≥ 200 copies/mL, or discontinuation for efficacy reasons, or premature discontinuations (not due to efficacy, adverse events or death), with last (single) VL ≥ 200 copies/mL; §Late switch to D/C/F/TAF arm week 96 results are based on patients who switched to D/C/F/TAF at week 52 (comprising 44 weeks of D/C/F/TAF exposure).

3.6. Safety and tolerability

D/C/F/TAF was well tolerated with 9% [66/763] serious AEs and 2% [17/763] AE-related discontinuations through 96 weeks in the D/C/F/TAF arm of which 5% (36/728) and 1% (5/728), respectively, occurred between weeks 48 and 96. In the late switch arm from week 52 through week 96, 6% [21/352] and 2% [7/352]) serious AEs and AE-related discontinuations occurred (Table 1). AEs at least possibly related to study drug were reported in 22% [165/763] of patients in the D/C/F/TAF arm over 96 weeks, and in 11% [38/352] of patients over 44 weeks of D/C/F/TAF treatment in the late switch arm. The most common AEs (all grades, ≥ 5% in both D/C/F/TAF and late switch arms) through week 96 were upper respiratory tract infection, viral upper respiratory tract infection, diarrhea and headache.

Most AEs, irrespective of causality, were grade 1 or 2. The most common grade 3 AE in the D/C/F/TAF arm was increased low-density lipoprotein-cholesterol (LDL-C), which was reported for 2 patients before week 48 and 2 patients after week 48 (both < 1%), and in the late switch arm from week 52 through week 96, pneumonia, tendon rupture, hypercholesterolemia, and depression, each reported for 2 patients (< 1%). Three cases of myocardial infarction (0.3%, 3/1080) occurred after week 48, including 2 in the D/C/F/TAF arm and 1 in the late switch arm.

Three deaths occurring after week 48 in the D/C/F/TAF arm were

Table 1
Overview of treatment-emergent AEs and laboratory abnormalities and median (IQR) change from baseline in lipids at Week 96.

	D/C/F/TAF Arm				Late Switch Arm		
	D/C/F/TAF (baseline – week 48) N = 763	D/C/F/TAF (week 48 – week 96) N = 728	D/C/F/TAF (baseline – week 96) N = 763	*P*-value[b,c]	bPI + F/TDF (baseline – week 52) N = 378	D/C/F/TAF[a] (week 52 –week 96) N = 352	*P*-value[b,c]
Patient years exposure[d]	689	664	1353		366	295	
Treatment-emergent AEs, n (%)							
AEs, any grade, regardless of causality	630 (83)	522 (72)	690 (90)	ND	316 (84)	258 (73)	ND
Study drug-related AEs	144 (19)	37 (5)	165 (22)	ND	28 (7)	38 (11)	ND
Grade 3–4 AEs regardless of causality	54 (7)	52 (7)	98 (13)	ND	31 (8)	26 (7)	ND
Study drug-related Grade 3 or 4 AEs	10 (1)	6 (1)	14 (2)	ND	4 (1)	7 (2)	ND
Serious AEs regardless of causality	35 (5)	36 (5)	66 (9)	ND	18 (5)	21 (6)	ND
Study drug-related serious AEs	1 (< 1)	1 (< 1)	2 (< 1)	ND	0	1 (< 1)	ND
AE-related discontinuations	12 (2)	5 (1)	17[e] (2)	ND	5 (1)	7[e] (2)	ND
Deaths	0	3[f] (< 1)	3[f] (< 1)	ND	0	0	ND
Most common AEs regardless of causality (≥10% D/C/F/TAF arm through 96 weeks)							
Upper respiratory tract infection	81 (11)	60 (8)	122 (16)	ND	39 (10)	30 (9)	ND
Viral upper respiratory tract infection	72 (9)	34 (5)	98 (13)	ND	40 (11)	25 (7)	ND
Diarrhea	60 (8)	26 (4)	80 (11)	ND	18 (5)	16 (5)	ND
Headache	58 (8)	25 (3)	79 (10)	ND	18 (5)	18 (5)	ND
Back pain	55 (7)	29 (4)	76 (10)	ND	23 (6)	12 (3)	ND
Study drug-related AEs (all grades; ≥ 1% either arm)							
Diarrhea	16 (2)	1 (< 1)	17 (2)	ND	2 (1)	4 (1)	ND
Headache	10 (1)	1 (< 1)	11 (1)	ND	0	1 (< 1)	ND
Abdominal pain	11 (1)	0	11 (1)	ND	0	0	ND
Osteopenia	5 (1)	0	5 (1)	ND	9 (2)	0	ND
Most common treatment-emergent grade 3 or 4 laboratory abnormalities (> 5% either arm)							
Fasting LDL-C (≥4.90 mol/L; ≥ 190 mg/dL)	47/737 (6)	38/688 (6)	67/741 (9)	ND	6/364 (2)	9/328 (3)	ND
Fasting total cholesterol (≥7.77 mol/L; ≥ 300 mg/dL)	27/737 (4)	16/692 (2)	36/741 (5)	ND	5/364 (1)	6/330 (2)	ND
Median (IQR) change in fasting lipids							
TC (mg/dL)	+19.9 (1.2; 39.4)	ND	+22.0 (−0.4; 44.0)	< 0.001	+1.3 (−12.0; 20.0)	+22.0 (3.0; 42.7)	< 0.001
HDL-C (mg/dL)	+2.7 (−3.0; 8.0)	ND	+3.0 (−2.0; 8.5)	< 0.001	0.0 (−4.6; 4.0)	+3.3 (−2.0; 8.0)	< 0.001
LDL-C (mg/dL)	+15.9 (0.0; 32.0)	ND	+17.0 (−3.0; 35.2)	< 0.001	+1.9 (−12.0; 17.0)	+15.0 (0.0; 32.9)	< 0.001
Triglycerides (mg/dL)	+5.7 (−21.0; 39.0)	ND	+7.0 (−25.0; 43.0)	< 0.001	+4.9 (−23.0; 39.0)	+8.0 (−25.8; 47.0)	0.004
TC/HDL-C ratio	+0.20 (−0.20; 0.60)	ND	+0.20 (−0.40; 0.70)	< 0.001	+0.10 (−0.30; 0.40)	+0.20 (−0.30; 0.70)	< 0.001

AEs, adverse events; IQR, interquartile range; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; ND, not determined.

[a] Comprising 44 weeks of D/C/F/TAF exposure (i.e. from the switch to D/C/F/TAF at week 52).

[b] Within treatment arm comparisons for change at week 96 from reference assessed by: Wilcoxon signed-rank test (eGFR, renal biomarkers and fasting lipids) and paired *t*-test (BMD).

[c] Reference for the D/C/F/TAF arm is study baseline and for the late switchers is the last value before the switch.

[d] Patient years of exposure = sum of treatment duration (in weeks) x 7/365.25.

[e] D/C/F/TAF arm: abdominal pain, diarrhea, gastrooesophageal reflux disease, pancreatitis, alanine aminotransferase increased, blood corticotrophin decreased, cortisol decreased, Hodgkin's disease, lymphoma, anxiety, depression suicidal, insomnia, Cushing's syndrome, edema peripheral, headache, urticaria, flushing (n = 1 each); myocardial infarction (n = 2), chronic kidney disease (n = 2; worsening of pre-existing chronic kidney disease in one patient prior to week 48 (Orkin et al., 2018) and chronic kidney disease in a participant after week 48); D/C/F/TAF late switch arm: vertigo, Cushing's syndrome, diarrhea, nausea, vomiting, malaria, pregnancy, depression, rash (n = 1 each).

[f] Three deaths were due to metastatic pancreatic carcinoma and 2 cases of myocardial infarction, 1 of which was in a patient who was a smoker, with an ongoing medical history of hyperlipidemia and hypertension and 1 was in a patient with an ongoing medical history of obesity and hypertension.

due to metastatic pancreatic carcinoma and 2 cases of myocardial infarction; 1 in a patient who was a smoker with an ongoing medical history of hyperlipidemia and hypertension and 1 patient with an ongoing medical history of obesity and hypertension. The only other serious AE deemed as possibly related to a study drug by the investigator and occurring after week 48 was grade 3 Cushing's syndrome in the late switch arm, which is likely explained by the administration of intramuscular corticosteroid injections.

Renal AEs regardless of causality occurred in 3% (20/763) of patients in the D/C/F/TAF arm over 96 weeks, and in 1% [5/352] of patients in the late switch arm from week 52 through week 96. Two grade 2, non-serious, related renal AEs led to discontinuation in the D/C/F/TAF arm over 96 weeks (Table 1 footnote). Neither renal AE met the criteria for proximal renal tubulopathy (PRT). No renal AEs led to discontinuation of D/C/F/TAF in the late switch arm or suggested treatment-emergent PRT.

Most treatment-emergent laboratory abnormality events were grade 1 or 2. Only grade 3 or 4 fasting LDL-C occurred in ≥5% of patients in the D/C/F/TAF arm over 96 weeks (9% [67/741]) (Table 1) of which 6% (38/688) occurred after week 48. No events occurred in ≥5% of patients in the late switch arm.

Median (IQR) change in body weight at week 96 was +1.8 (−0.8; 4.6) kg versus baseline in the D/C/F/TAF arm and +1.6 (−0.4; 3.5) kg versus the value prior to switching in the late switch arm.

3.6.1. Laboratory parameters

Fasting lipid parameters remained stable after week 48 in the D/C/F/TAF arm and increased from the value prior to switching to week 96 in the late switch arm. The change in TC/HDL-C ratio from the value prior to switching in the late switch arm was +0.20, while the ratio in the D/C/F/TAF arm remained stable after week 48 (all changes $P < 0.005$) (Table 1 and Supplementary Fig. 1). During treatment, lipid-lowering drugs were started by 32/763 (4%) and 59/763 (8%) of patients by weeks 48 and 96, respectively, in the D/C/F/TAF arm, and by 3% (11/378) and 5% (19/352), respectively, in the control arm.

In the D/C/F/TAF arm, median (IQR) change from baseline to week 96 in $eGFR_{cr}$ was −1.3 (−8.3; 5.1) mL/min/1.73 m^2 (Fig. 4A) ($P < 0.001$). Median change from the value prior to switching to week 96 in $eGFR_{cr}$ was −0.7 (−6.9; 4.9) mL/min/1.73 m^2 in the late switch arm ($P = 0.007$) (Fig. 4A). Median changes in $eGFR_{cyst}$ were similar (Fig. 4B).

In the D/C/F/TAF arm, improvements in renal biomarkers seen at 48 weeks compared with baseline were maintained through week 96 (Supplementary Fig. 2A). Median (IQR) changes from baseline to week

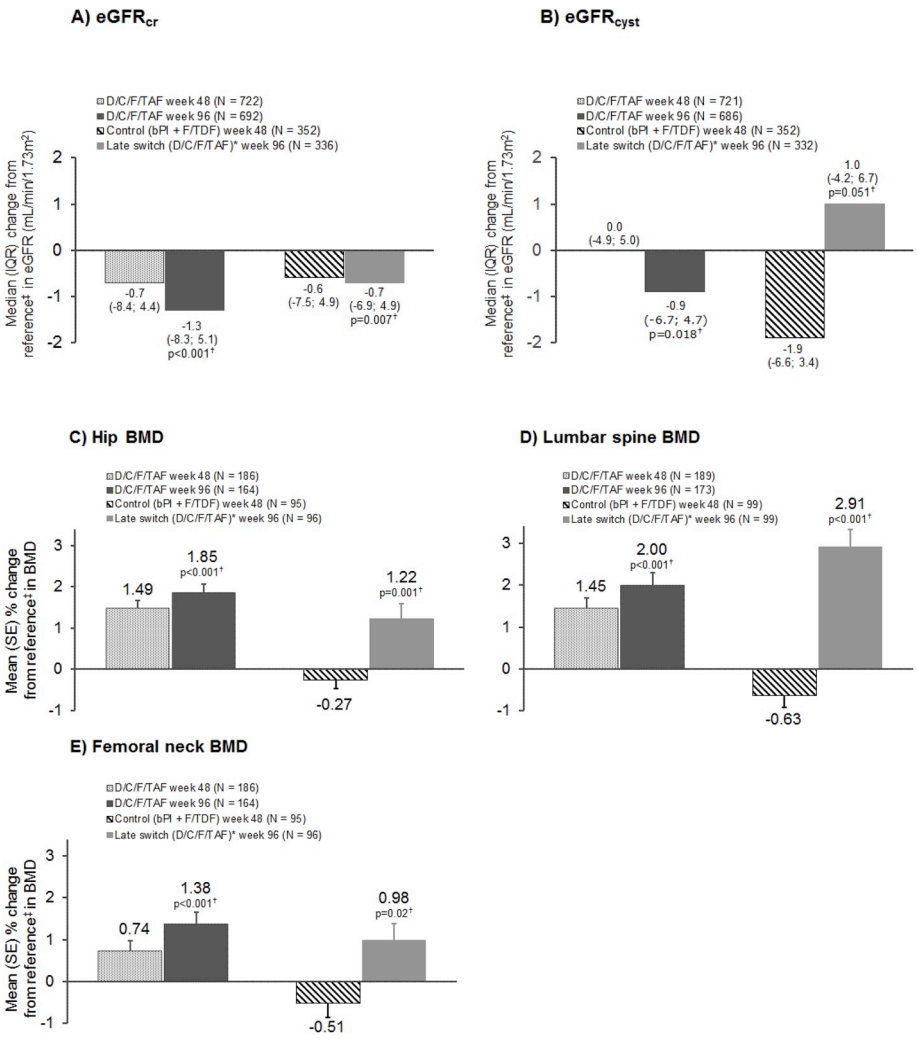

Fig. 4. Change from reference to week 48 and week 96 in renal and bone parameters. A) $eGFR_{cyst}$, B) $eGFR_{cr}$ and BMD of the C) hip, D) lumbar spine, and E) femoral neck.

*Comprising ~44 weeks of D/C/F/TAF exposure (i.e. from the switch to D/C/F/TAF at week 52). †Within treatment arm change from reference assessed by Wilcoxon signed-rank test (eGFR) and paired t-test (BMD). ‡Reference for D/C/F/TAF and control is baseline and for late switch (D/C/F/TAF) is the last value before the switch.

96 were −22.2 (−51.5; −3.5) mg/g for UPCR, −0.6 (−3.7; 1.2) mg/g for UACR, −25.1 (−106.4; 13.1) μg/g for RBP:Cr and −68.2 (−386.6; −11.0) μg/g for B2M:Cr (all $P < 0.001$ vs. baseline). In the late switch arm, significant improvements at week 96 versus the value prior to switching (all $P < 0.001$) were seen for median (IQR) changes in UPCR [–12.8 (−48.2; 6.4) mg/g], UACR [–0.9 (−6.0; 1.1) mg/g], RBP:Cr [–39.1 (−200.1; 4.3) μg/g] and B2M:Cr [–110.3 (−496.8; −18.3) μg/g] (Supplementary Fig. 2A).

3.6.2. Bone substudy

The bone substudy included 209 patients in the D/C/F/TAF arm and 108 in the control arm (Orkin et al., 2018). Over 96 weeks, there were sustained improvements in BMD at the hip (+1.85% at week 96 vs. baseline; Fig. 4C), lumbar spine (+2.00%; Fig. 4D), and femoral neck (+1.38%; Fig. 4E) in the D/C/F/TAF arm (all $P < 0.001$ vs. baseline, paired *t*-test). Similar significant improvements in BMD at week 96 compared with the value prior to switching were seen in the late switch arm (Fig. 4C–E).

In the D/C/F/TAF arm, the proportion of patients who had a ≥3% decrease or increase in hip, lumbar spine, and femoral neck BMD at week 96 versus baseline was stable through week 96 (Supplementary Table 6). In the late switch arm, more patients had a ≥3% increase in BMD at each site over 44 weeks of D/C/F/TAF treatment than over the first 48 weeks of bPI plus F/TDF therapy, and fewer patients had a ≥3% decrease in BMD (Supplementary Table 6). Conclusions were similar for increases or decreases of ≥5% or ≥7% in BMD, as well for the proportions of patients with an improvement (osteopenia to normal or osteoporosis to normal or osteopenia) or a decline (normal to osteopenia or normal or osteopenia to osteoporosis) in BMD clinical status (Supplementary Table 6).

Changes in bone biomarkers overs weeks 52–96 in the late switch arm were similar to those reported by week 48 in the D/C/F/TAF arm (Supplementary Fig. 2B).

4. Discussion

The week 96 analysis of this phase 3, randomized, open-label trial showed that a low proportion of treatment-experienced, virologically suppressed HIV-1-positive adults in the D/C/F/TAF arm had PDVR (≥50 copies/mL) cumulative through 96 weeks (3.1%) and a high proportion (90.7%) remained suppressed (VL < 50 copies/mL) at week 96, with few patients (1.2%) having VL ≥ 50 copies/mL (FDA-snapshot analysis). Virologic rebound mainly consisted of low-level and transient viremia, with very few PDVRs ≥200 copies/mL (0.5%). More than half of patients in the D/C/F/TAF arm with PDVR ≥50 copies/mL achieved resuppression by week 96, without a change in therapy. In the late switch arm, only 2.3% had PDVR cumulative through 44 weeks, and virologic suppression was also sustained at week 96 (93.8%) with 1.7% of patients having VL ≥ 50 copies/mL (FDA snapshot), consistent with week 48 results in the D/C/F/TAF arm. Importantly, through week 96 no patients needed to discontinue D/C/F/TAF due to lack of efficacy. Results were consistent across baseline patient subgroups, in the per-protocol PDVR and FDA-snapshot analyses and using the 200 copies/mL cutoff.

While considering differences in study designs when making comparisons, entry criteria were less restrictive than in other switch studies with comparable or lower response rates e.g. for bictegravir (Daar et al., 2018; Molina et al., 2018), dolutegravir (Joly et al., 2017; Llibre et al., 2018; Taiwo et al., 2018; Trottier et al., 2017), and atazanavir (Di Giambenedetto et al., 2017; Perez-Molina et al., 2015). In EMERALD, there was no exclusion based on previous VF or RAMs, except for history of VF on DRV-based regimens or DRV RAMs if historical genotypes were available. However, it should be noted only ≥3 DRV RAMs is correlated with DRV resistance (de Meyer et al., 2008). N(t)RTI RAMs, including emtricitabine or tenofovir RAMs, were not an exclusion criterion. The proportion of patients achieving VL < 50 copies/mL at 96 weeks was similar to week 96 response rates in other HIV studies evaluating switching to integrase inhibitor-based regimens (Aboud et al., 2018; Gatell et al., 2019).

PDVR and response rates should be placed in the context that these patients were treatment experienced, with 58% of patients having received ≥5 previous antiretroviral agents, and 15% having previous antiretroviral VF. Previous antiretroviral use and VF did not affect PDVR and response rates.

No patient developed resistance to any of the study drugs through week 96 despite a cumulative 1648 patient-years of exposure to D/C/F/TAF. This is consistent with previous DRV and D/C/F/TAF studies (Eron et al., 2018; Lathouwers et al., 2017), further supporting the high genetic barrier to resistance of DRV.

D/C/F/TAF was generally well tolerated through 96 weeks, with low incidences of discontinuations due to AEs (2%) that were numerically lower than incidences seen in integrase inhibitor-based regimen switching studies over 96 weeks (Aboud et al., 2018; Gatell et al., 2019). The D/C/F/TAF tolerability profile at week 96 was consistent with the week 48 analyses of EMERALD (Orkin et al., 2018) and AMBER (Eron et al., 2018).

The small increase in body weight in the D/C/F/TAF arm over 2 years (1.8 kg) is consistent with previous studies of patients receiving ART (Taramasso et al., 2017), and may be due in part to lifestyle changes and improved disease control. Weight gains were numerically larger over 9–18 months when switching to integrase inhibitor-based ART, particularly for dolutegravir (Menard et al., 2017; Norwood et al., 2017).

Renal, bone, and lipid safety were consistent with the established effects of TAF versus TDF and cobicistat (DeJesus et al., 2018; Eron et al., 2018; Orkin et al., 2018; Raffi et al., 2017; Wohl et al., 2016). Small decreases in $eGFR_{cr}$ in both arms were well within normal limits and possibly due to the effect of cobicistat on inhibition of tubular secretion of creatinine without reducing actual GFR (Elion et al., 2011; Gallant et al., 2013; German et al., 2012). When measuring GFR with cystatin C, which is not affected by the interaction of cobicistat with creatinine secretion (Laterza et al., 2002), changes were also small, with all results remaining within normal limits.

Improvements in renal tubular proteinuria and bone parameters were maintained in the D/C/F/TAF arm and seen in the late switch arm from week 52 to week 96, suggesting that D/C/F/TAF has a lower potential for nephrotoxicity and bone loss than the control regimen. These renal tubular proteinuria and bone safety results are consistent with the week 48 results in the D/C/F/TAF arm of EMERALD (Orkin et al., 2018) and AMBER (Eron et al., 2018) and week 96 analyses of previous phase 3 studies in virologically suppressed patients who switched from a TDF- to a TAF-containing regimen (DeJesus et al., 2018; Raffi et al., 2017; Wohl et al., 2016), including a pooled analysis of 5 phase 3 studies (Rockstroh et al., 2017).

In the D/C/F/TAF arm, fasting lipid levels remained stable after week 48 with minimal increases in the late switch arm and an identical change in TC/HDL-C ratio (+0.2) in both arms at week 96. Only a small proportion of patients initiated lipid-lowering therapy in both arms.

A study limitation was the lack of a control arm in the week 96 analysis, as patients in both arms were switched to D/C/F/TAF. Other limitations, as at week 48, include the lack of power to assess efficacy in patient subgroups and assessment of bone parameters in only a subset of participants.

In conclusion, in virologically suppressed, treatment-experienced, HIV-positive adults, including those with prior VF and archived resistance, switching to the D/C/F/TAF STR resulted in low PDVR rates cumulative through 96 weeks (3% D/C/F/TAF; 2% late switch) and maintenance of high virologic suppression rates (> 90%) at week 96. Efficacy and safety results in the late switch arm were consistent with week 48 results in the D/C/F/TAF arm. No patients discontinued for efficacy-related reasons, and no drug resistance mutations developed. D/C/F/TAF was well tolerated over 96 weeks with bone, renal and lipid

safety consistent with known profiles of the D/C/F/TAF components. Results of EMERALD through 96 weeks confirm the efficacy, high genetic barrier to resistance and safety advantages of D/C/F/TAF, even in patients with a history of non-DRV VF.

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Contributors

JJE, CO, DC, F Pulido, F Post and SDW were investigators in the trial and reported data for those patients. EL, VH, RP, KB and EVL were involved in the data analyses. All authors were involved in the development of the primary manuscript, interpretation of data, and have read and approved the final version, and have met the criteria for authorship as established by the ICMJE.

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Appendix A. Supplementary data

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