P222

Long-term Efficacy and Resistance Analyses of D/C/F/TAF in the Phase 3 AMBER and EMERALD Studies: Post 96-week Data

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Background & Objective

- In the two phase 3 randomized active controlled non-inferiority trials, AMBER (NCT02431247) and EMERALD (NCT02269917), darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) demonstrated non-inferior efficacy versus the control arms at Week (wk) 48, and a high virologic response rate and a low virologic failure (VF) rate through wk 96 (**Table 1**), with low rates of discontinuations due to adverse events, a high genetic barrier and a favorable safety profile in antiretroviral treatment (ART)-naïve and -experienced, virologically-suppressed HIV-1-infected adults.[1,2,3]
- Here, we evaluated the long-term efficacy and the resistance to D/C/F/TAF treatment beyond wk 96.

Table 1. Summary of Wk 48 and Wk 96 Efficacy Results in AMBER and EMERALD Studies (ITT)[1,2,4,5]

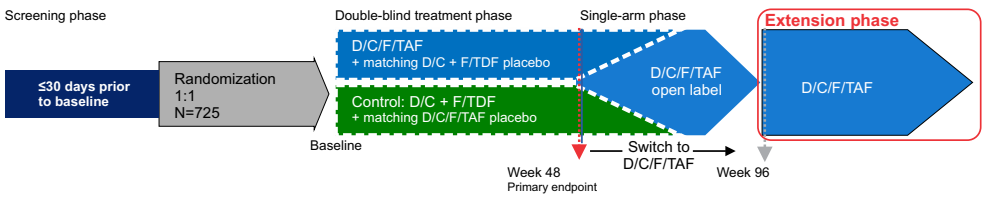
AMBER in ART-naïve adults				
% (95% CI)[a]		D/C/F/TAF (N=362)	Control (D/C + F/TDF) – Switch to D/C/F/TAF (N=363)	D/C/F/TAF-control[b] Difference (95% CI)
Primary outcome				
Virologic response (FDA Snapshot; VL <50 copies/mL)	Wk 48	91 (88; 94)	88 (85; 92)	3 (–2; 7; p<0.0001)
	Wk 96	85 (81; 89)[c]		
VF (FDA Snapshot; VL ≥50 copies/mL)[d]	Wk 48	4 (3; 7)	3 (2; 6)	
	Wk 96	6 (3; 8)[c]		
EMERALD in ART-experienced, virologically-suppressed adults				
% (95% CI)[a]		Initial Switch to D/C/F/TAF (N=763)	Control (bPI + F/TDF) – Late Switch to D/C/F/TAF (N=378)	D/C/F/TAF-control[e] Difference (95% CI)
Primary outcome				
PDVR (cumulative confirmed VL ≥50 copies/mL)	Through wk 48	2 (2; 4)	2 (1; 4)	<1 (–2; 2; p<0.0001)
	Through wk 96	3 (2; 5)[c]		
Secondary outcome				
Virologic response (FDA Snapshot; VL <50 copies/mL)	Wk 48	95 (93; 96)	94 (91; 96)	1 (–2; 4)
	Wk 96	91 (88; 93)[c]		
VF (FDA Snapshot; VL ≥50 copies/mL)[d]	Wk 48	1 (<1; 2)	1 (<1; 2)	<1 (-1; 1)
	Wk 96	1 (1; 2)[c]		

ART = antiretroviral therapy; bPI = boosted protease inhibitor; CI = confidence interval; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide once-daily; D/C + F/TDF = darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate once-daily; PDVR = protocol-defined virologic rebound (cumulative confirmed VL ≥50 copies/mL or premature discontinuation with last VL ≥50 copies/mL); VF = virologic failure; VL = viral load
[a]Two-sided Exact Clopper-Pearson 95% CI; [b]Calculated with Mantel–Haenszel test adjusting for screening VL (≤ or >100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/mL); [c]Focus is on the results of the Week 96 D/C/F/TAF arm, and due to the lack of an appropriate comparator beyond Week 48, only the efficacy results for the D/C/F/TAF arms are presented; [d]Last VL in Week 48 or 96 window ≥50 copies/mL, or discontinuation for efficacy reasons, or premature discontinuations (#efficacy/adverse events/death), with last available VL ≥50 copies/mL; [e]Based on Mantel–Haenszel test adjusting for bPI at screening

Methods

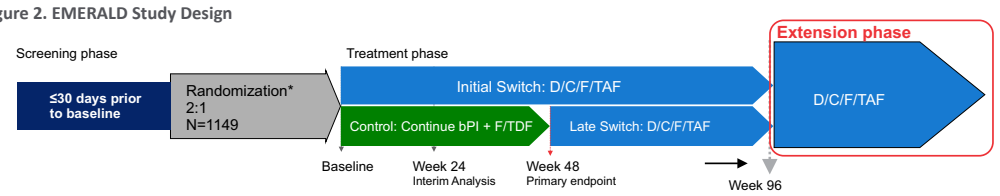
In **AMBER,** treatment-naïve adults with HIV-1 were randomized to D/C/F/TAF group or switch to D/C/F/TAF group (Control group: darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate once daily [D/C + F/TDF], followed by a switch to open-label D/C/F/TAF after wk 48).

Figure 1. AMBER Study Design



In **EMERALD,** virologically suppressed, treatment-experienced adults with HIV-1 were randomized to initial switch to D/C/F/TAF group or late switch to D/C/F/TAF group (Control group: continuing a boosted protease inhibitor with F/TDF and then switched to D/C/F/TAF at wk 52).

Figure 2. EMERALD Study Design



*Previous ART virologic failure allowed absence of history of failure on DRV treatment and absence of DRV RAMs, if historical genotype available
ART = antiretroviral therapy; bPI = boosted protease inhibitor; DRV, darunavir; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide once-daily; D/C + F/TDF = darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate once-daily.

- During the post-wk 96 extension phase, patients attended visits every 6 months (m). Patients exited the study when commercially available D/C/F/TAF became available, when they switched to other ARTs or discontinued.
- Plasma viral load levels were measured by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® Taqman® HIV-1 Test, v2.0 assay.
- Proportion of patients with HIV-1 RNA <50 copies/mL (observed case) post-wk 96 in all treatment groups was analyzed.
- Immunologic change post-wk 96 was determined by changes in absolute CD4+ cell count in all treatment groups.
- Resistance development post-wk 96 and overall is presented:
  - For AMBER (ART-naïve patients): At screening, genotypic resistance testing was performed using GenoSure®MG (HIV-1 protease [PR]/reverse transcriptase [RT] genotype assay; Monogram Biosciences, South San Francisco, CA, USA). Post-baseline PhenoSense®GT (combined HIV-1 PR/RT genotype/phenotype) was performed in patients with protocol-defined virologic failure (PDVF: Virologic nonresponse, virologic rebound and/or VL ≥400 copies/mL at study endpoint or discontinuation) with VL ≥400 copies/mL (resistance assay cut-off) at failure (confirmed or unconfirmed) or at later time points.
  - For EMERALD (virologically-suppressed, ART-experienced patients): Post-baseline GenoSure®MG was performed in patients with protocol defined virologic rebound (PDVR) (cumulative confirmed VL ≥50 copies/ mL) and a VL ≥400 copies/mL at failure (confirmed or unconfirmed) or at later time points, including those who discontinued with a last single VL ≥400 copies/mL.

Results

Study Termination

- In AMBER, 311 patients in the D/C/F/TAF group and 310 in the switch to D/C/F/TAF group continued D/C/F/TAF treatment in the extension phase of which 290 (93.2%) and 284 (91.6%), respectively, completed the study.
- In EMERALD, 699 patients in the initial switch to D/C/F/TAF group and 337 in the late switch to D/C/F/TAF group continued with D/C/F/TAF treatment in the extension phase of which 648 (92.7%) and 314 (93.2%), respectively, completed the study.
- The mean D/C/F/TAF exposure post-wk 96 was 67.4 and 71.5 weeks in the D/C/F/TAF and switch to D/C/F/TAF group, respectively in AMBER and ~84 wks for both groups in EMERALD.

Table 2. Week 96 to End of Extension Study Termination (ITT)

	AMBER		EMERALD	
	D/C/F/TAF[a]	Switch to D/C/F/TAF[b]	Initial Switch to D/C/F/TAF[c]	Late Switch to D/C/F/TAF[d]
Analysis set: ITT, N	311	310	699	337
Completed	290 (93.2%)	284 (91.6%)	648 (92.7%)	314 (93.2%)
Switched to Commercial Symtuza	270 (86.8%)	258 (83.2%)	554 (79.3%)	272 (80.7%)
Switched to ARTs other than Symtuza[e]	20 (6.4%)	26 (8.4%)	94 (13.4%)	42 (12.5%)
Discontinued*	45 (12.4%)	26 (8.4%)	51 (7.3%)	23 (6.8%)
Patient did not fulfill all inclusion/ exclusion criteria	0	0	0	0
Death	0	1 (0.3%)	1 (0.1%)	1 (0.3%)
Lost to follow-up	4 (1.3%)	7 (2.3%)	11 (1.6%)	7 (2.1%)
Non-compliance with study drug	0	0	1 (0.1%)	0
Adverse event	4 (1.3%)	4 (1.3%)	9 (1.3%)	5 (1.5%)
Physician decision	2 (0.6%)	2 (0.6%)	3 (0.4%)	1 (0.3%)
Pregnancy	0	0	0	1 (0.3%)
Product quality complaint	0	0	0	0
Study terminated by sponsor	0	0	0	0
Withdrawal by patient	5 (1.6%)	10 (3.2%)	17 (2.4%)	4 (1.2%)
Other	6 (1.9%)	3 (1.0%)	9 (1.3%)	4 (1.2%)

N = number of patients with data, n = number of patients with that observation; ART = antiretroviral therapy; D/C/F/TAF = darunavir cobicistat/emtricitabine/tenofovir alafenamide once-daily; ITT = Intention to Treat
* Patients who discontinued because Symtuza was not available at time of study completion are considered as completed.
[a] Patients who started on D/C/F/TAF.
[b] Patients who started on DRV/COBI + FTC/TDF followed by a switch to open-label D/C/F/TAF after wk 48.
[c] Patients who switched to D/C/F/TAF at baseline.
[d] Patients who continued their bPI+F/TDF regimen; followed by a switch to open label D/C/F/TAF at wk 52.
[e] Patients for whom Symtuza was not available at time of study completion.

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Efficacy data

Table 3. Proportion of Patients with HIV RNA <50 Copies/mL (Observed Case) by Analysis Time Point in the Post-wk 96 Extension Phase

	AMBER		EMERALD	
	D/C/F/TAF	Switch to D/C/F/TAF	Initial Switch to D/C/F/TAF	Late Switch to D/C/F/TAF
Analysis set: ITT, N	311	310	699	337
Week 96 + 6 months (N)	303	296	688	334
<50 copies/mL, n (%)	296 (97.7)	285 (96.3)	673 (97.8)	327 (97.9)
Week 96 + 12 months (N)	194	214	611	302
<50 copies/mL, n (%)	192 (99.0)	207 (96.7)	601 (98.4)	294 (97.4)
Week 96 + 18 months (N)	158	167	461	225
<50 copies/mL, n (%)	155 (98.1)	164 (98.2)	459 (99.6)	222 (98.7)
Week 96 + 24 months (N)	81	92	280	134
<50 copies/mL, n (%)	79 (97.5)	88 (95.7)	278 (99.3)	132 (98.5)
Week 96 + 30 months (N)	57	58	135	64
<50 copies/mL, n (%)	54 (94.7)	53 (91.4)	134 (99.3)	64 (100)
Week 96 + 36 months (N)	19	16*	52	26
<50 copies/mL, n (%)	19 (100.0)	11 (68.8)	51 (98.1)	26 (100)
Week 96 + 42 months (N)	NA	NA	16	7
<50 copies/mL, n (%)	NA	NA	16 (100)	7 (100)

*Of the 5 patients with HIV RNA ≥50 copies/mL, 3 had HIV RNA <200 copies/mL and 2 had HIV RNA ≥200 copies/mL (i.e. 12300 cp/ml and 243 cp/mL, respectively)
D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide once-daily; ITT = intention to treat; NA, not applicable

Immunology Data

Table 4. Actual CD4+ Cell Counts by Analysis Time Point in the Post-wk 96 Extension Phase; ITT

	AMBER		EMERALD	
	D/C/F/TAF	Switch to D/C/F/TAF	Initial Switch to D/C/F/TAF	Late Switch to D/C/F/TAF
Mean (SE) baseline/reference* CD4+ count, cells/mm³	497.3 (12.44)	695.0 (16.41)	653.3 (9.12)	652.0 (13.57)
Mean (SE) baseline CD4+ count at wk 96 + 6 months, cells/mm³	790.2 (17.23)	749.7 (16.44)	706.4 (10.51)	681.3 (14.99)

CD4+ cell count remained stable beyond the wk 96 + 6-month time point in both studies up until + 36m in AMBER and + 42m in EMERALD

*mean (SE) reference CD4+ count value for switch to D/C/F/TAF group (i.e. last value prior to the switch to D/C/F/TAF)
D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide once-daily; ITT = Intention to Treat; SE = standard error

Resistance Data:

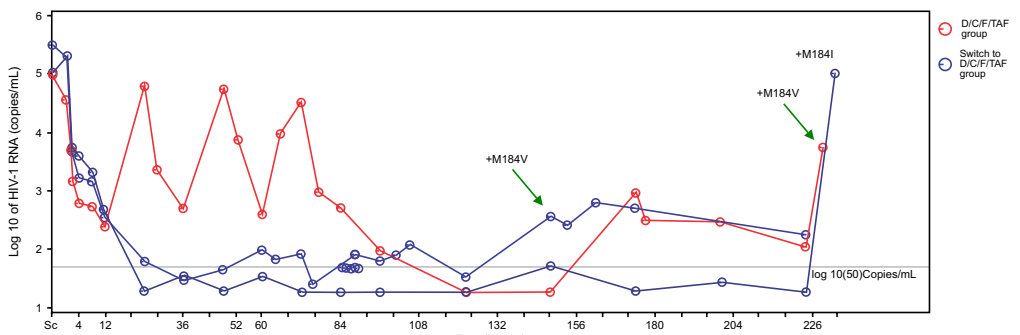
AMBER

- **Post-wk 96,** 3 (1.0%) patients in the D/C/F/TAF group and 6 (2.1%) patients in the switch to D/C/F/TAF group showed first PVDF and 2 and 6 patients had post-wk 96 genotypes/phenotypes available, respectively.
- None developed darunavir (DRV) or tenofovir (TFV) (delivered as TDF or TAF) resistance-associated mutations (RAMS) and 3 patients developed mutations at RT position 184 (conferring resistance to emtricitabine (FTC) and lamivudine (3TC; **Figure 3**).
  - 1 patient in D/C/F/TAF group developed M184V.
  - 2 patients in switch to D/C/F/TAF group developed M184I or V.
    - One additional patient in switch to D/C/F/TAF group developed an International AIDS Society [IAS]-USA primary protease inhibitor (PI) RAM at wk 96+ 18 m: M46I (not a DRV RAM) and one IAS-USA secondary PI - RAM L10F, conferring resistance to nelfinavir (NFV) and partial sensitivity to fosamprenavir (fAPV), but retaining sensitivity to all other PIs (Note: patient's HIV also had 4 IAS-USA secondary PI RAMs at screening: M36I, H69K, V77V/I, and L89M).

EMERALD

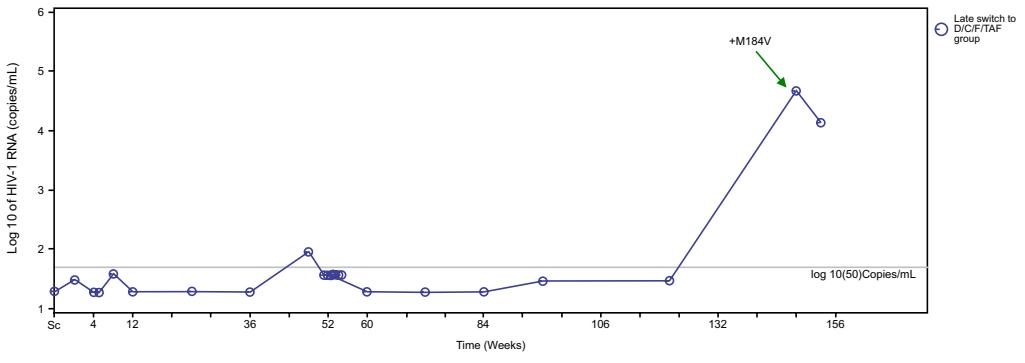
- **Post-wk 96**, in total 18 (2.7%) of the 671 patients at risk in the initial switch to D/C/F/TAF group and 7 (2.2%) of the 323 patients in the late switch to D/C/F/TAF group showed first PDVR. Due to low viral load values, only 6 PDVR in the initial switch to D/C/F/TAF group and 5 PDVR in the late switch to D/C/F/TAF group had post-wk 96 genotypes.
- No DRV or TFV RAMs were observed (**Figure 4**).
  - 1 patient in the late switch to D/C/F/TAF group had M184V (genotypic resistance to 3TC, FTC, partial resistance to didanosine (DDI) and abacavir (ABC); patient also had transmitted IAS-USA non-nucleoside reverse transcriptase inhibitors (NNRTI) RAMs K103N and P225H (resistance to nevirapine [NVP] and efavirenz [EFV]).
    - One additional patient in the initial switch to D/C/F/TAF group had a primary PI RAM D30D/N (not a DRV RAM) and 3 thymidine analog mutations (TAMs) at wk 96 + 6 m: D67D/N, K70K/R, and K219K/E (genotypic resistance to NFV [nelfinavir], AZT [zidovudine] and partial sensitivity to TFV, related to VF on previous treatment, including ABC, AZT, 3TC, DDI, and NFV).

Figure 3. Individual Viral Load Profiles of AMBER Patients with Observed or Emerging RAMs While on D/C/F/TAF



D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HIV = human immunodeficiency virus type 1; RAMs = resistance-associated mutations; RNA = ribonucleic acid

Figure 4. Individual Viral Load Profiles of EMERALD Patients With Observed or Emerging RAMs While on D/C/F/TAF



D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HIV = human immunodeficiency virus type 1; RAMs = resistance-associated mutations; RNA = ribonucleic acid

Over the whole treatment period, from baseline to the end of the extension phase, in both studies, none of the patients developed DRV or TFV RAMs.

- **2 patients in the D/C/F/TAF group and 3 in the switch to D/C/F/TAF group developed FTC RAM M184I/V in AMBER and 1 EMERALD patient in late switch to D/C/F/TAF group developed FTC RAM M184V.**

Conclusions

In AMBER (treatment-naïve adults) and EMERALD (treatment-experienced, virologically suppressed adults), long-term D/C/F/TAF treatment was considered efficacious with a high genetic barrier to resistance development

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