SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
SYMTUZA - EMERALD Study

Study Overview[a,b]

EMERALD

Phase 3, randomized, active-controlled, open-label, **noninferiority study**

Evaluated efficacy, safety, and tolerability of switching to **D/C/F/TAF vs** continuing **bPI + FTC/TDF**

Virologically suppressed, **treatment-experienced**, HIV-1-infected **adults**

N=1141

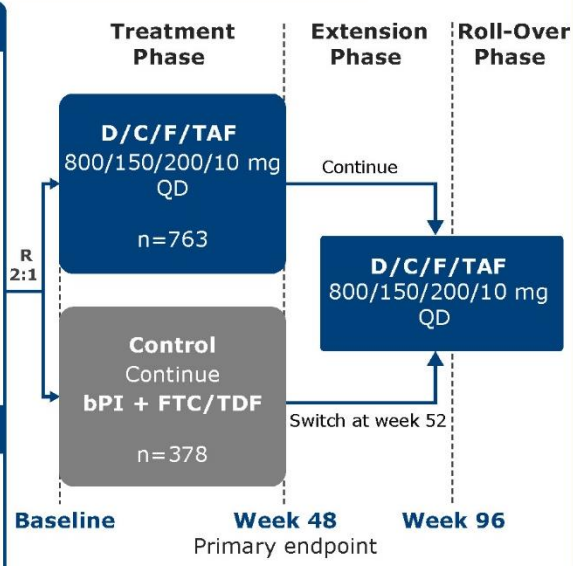
Study Design[a,b]

Key Inclusion Criteria

- **Virologically suppressed adults:** ≥1 VL <50 copies/mL ≤2 months before screening
- **Stable ARV regimen** ≥6 months of FTC/TDF + bPI comprising:
  - DRV/r or DRV/c QD,
  - ATV/r or ATV/c QD, or
  - LPV/r BID
- CrCl ≥50 mL/min

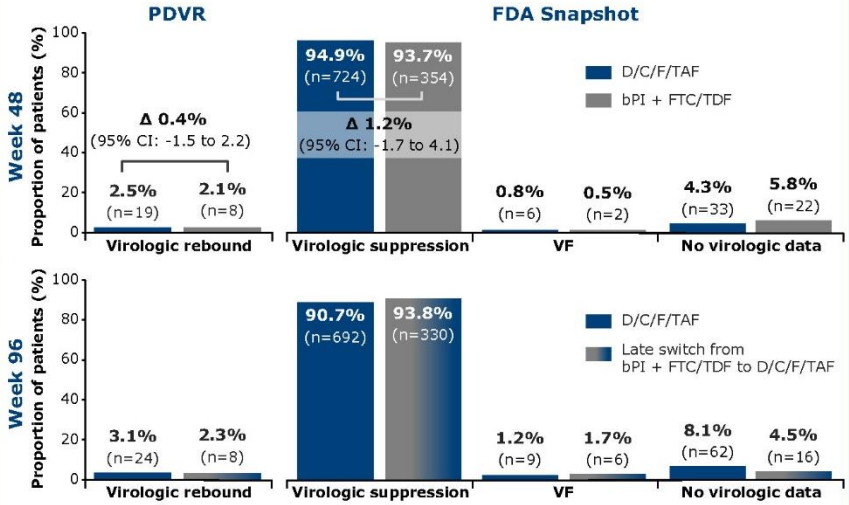
Key Exclusion Criteria

- **DRV RAMs** or DRV-based failure
- Hepatitis B or C coinfection



Efficacy

- **Primary endpoint**: Noninferiority of **D/C/F/TAF vs bPI + FTC/TDF** for virologic rebound through **week 48** was met[a,b]



- Virologic response rates through week 96 were consistent across subgroups and were not affected by prior VF or previous ARV experience[b]

Safety and Tolerability

- **Common AEs** (≥10% D/C/F/TAF arm through 96 weeks):[b]
  - Upper respiratory tract infection (16%)
  - Viral upper respiratory tract infection (13%)
  - Diarrhea (11%)
  - Headache (10%)
  - Back pain (10%)
- **AE-related discontinuations** were reported in 2% of patients in the D/C/F/TAF arm through week 96[b]
- Through week 96, improved **renal and bone safety** outcomes were observed with D/C/F/TAF vs control[b]

Header sections within the image contain hyperlinks to related sections within the document.

Abbreviations: AE, adverse event; ARV, antiretroviral; ATV, atazanavir; BID, twice daily; bPI, boosted protease inhibitor; c, cobicistat; CI, confidence interval; CrCl, creatinine clearance; D/C/F/TAF, darunavir, cobicistat, emtricitabine, and tenofovir alafenamide; DRV, darunavir; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate; FDA, Food and Drug Administration; HIV-1, human immunodeficiency virus type 1; LPV, lopinavir; PDVR, protocol-defined virologic rebound; QD, once daily; r, ritonavir; RAM, resistance-associated mutation; VF, virologic failure; VL, viral load.

[a]Orkin (2018). [b]Eron (2019)

SUMMARY

- The EMERALD study is a phase 3, randomized, active-controlled, open-label noninferiority study to evaluate the efficacy, safety, and tolerability of switching to SYMTUZA vs continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type-1 (HIV-1)-infected adults.[1,2]
- At week 48, the proportion of patients with confirmed virologic rebound (primary endpoint) was 2.5% for the SYMTUZA group and 2.1% for the bPI group.[1]
- Virologic response rates at week 48 were 94.9% for the SYMTUZA group and 93.7% for the bPI group.[1]
- There were no differences between age, gender, and race subgroups in terms of virologic rebound, renal, and bone safety.[3]
- In another subgroup analysis, results were consistent regardless of prior virologic failure (VF) and prior experience with multiple antiretrovirals (ARVs).[3]
- At week 96, in the SYMTUZA arm, the rates of protocol-defined virologic rebound (PDVR), virologic suppression, and VF were 3.1%, 90.7%, and 1.2%, respectively.[2]
- Efficacy and safety results through week 96 in the subgroups of age, gender, race, number of previous ARVs used, previous VF, screening bPI, and screening boosting agent were consistent with the results in the overall population.[4]

CLINICAL DATA

EMERALD STUDY

The EMERALD study is a phase 3, randomized, active-controlled, open-label noninferiority study to evaluate the efficacy, safety, and tolerability of switching to SYMTUZA vs continuing the current regimen consisting of a bPI combined with FTC/TDF in virologically-suppressed, HIV-1-infected adults.[1,2]

Study Design/Methods

- Select inclusion criteria: virologically suppressed adults (≥1 viral load [VL] <50 copies/mL within 2 months before screening); receiving a stable ARV regimen containing darunavir (DRV)/ritonavir(r) or DRV/cobicistat (COBI) once daily, atazanavir/r (ATV/r) or ATV/COBI, or lopinavir/r (LPV/r) plus FTC/TDF for ≥6 months; no DRV resistance-associated mutations (RAMs) or history of DRV failure; creatinine clearance ≥50 ml/min.
- Patients with active clinically significant diseases or who were hepatitis B or C positive were excluded.
- Medications or herbal supplements known/suspected to interact with study medication were not allowed.
- Patients were stratified according to protease inhibitor (PI) and then randomized 2:1 to switch to a single-tablet regimen consisting of SYMTUZA (DRV 800 mg, COBI 150 mg, FTC 200 mg, and tenofovir afenamide [TAF] 10 mg) or to continue their bPI regimen. At week 52, patients could continue on SYMTUZA (SYMTUZA arm) or switch from bPI combined with FTC/TDF to SYMTUZA (late switch arm, 44 weeks of SYMTUZA exposure) in an extension phase until week 96.
- Primary endpoint: proportion of patients in the intention-to-treat (ITT) population with virologic rebound through week 48 (per-protocol analysis was also performed).
    - Virologic rebound was defined as confirmed VL ≥50 copies/mL or premature discontinuations (irrespective of reason) with last VL ≥50 copies/mL through week 48.
    - Non-inferiority margin: upper limit of 95% confidence interval (CI) <4% at week 48.
- Secondary endpoints included VL <20, <50, and <200 copies/mL at week 48 (Food and Drug Administration [FDA] snapshot); change from baseline in CD4+ count, serum

creatinine, estimated glomerular filtration rate (eGFR), and renal biomarkers; grade 3-4 adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation; development of resistance VFs; adherence.
- A bone investigation substudy was also conducted.
  - Dual-energy X-ray absorptiometry (DXA) scans for hip, lumbar spine, and femoral neck bone mineral density (BMD) were performed at baseline, 24 weeks, and 48 weeks.
  - Secondary endpoints included percentage change from baseline in BMD, changes in associated T-score, and changes in bone biomarkers.
- HIV proviral DNA was analyzed retrospectively using GenoSure Archive® on baseline samples for patients with PDVR (confirmed VL ≥50 copies/mL) or prior VF.[5]
- GenoSure® MG was used for post-baseline genotypic resistance testing of patients with PDVR and a VL ≥400 copies/mL.[5]

Results

- A total of 1141 patients (n=763 SYMTUZA, n=378 bPI) were randomized and included in the ITT population.
- Of these, 95% (1087/1141) completed 48 weeks of therapy.
- Of the 1141 patients randomized and treated, 1080 (95%) continued in the extension phase (N=728 SYMTUZA [95%]; N=352 late switch [93%]), with 1036 patients (91%) on study treatment through 96 weeks.
- 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, with a similar proportion between arms (4%).

Baseline Characteristics

- Baseline characteristics were similar between groups (see Table: Baseline Characteristics).
- Overall, 15% (n=169) of patients had previous VF (7% on a PI, 11% on a nucleoside reverse transcriptase inhibitor [NRTI], 6% on a nonnucleoside reverse transcriptase inhibitor [NNRTI], and 1% on an integrase strand transfer inhibitor [INSTI]).[5]

Baseline Characteristics[1]

Demographics	SYMTUZA (N=763)	bPI (N=378)
Age, median (IQR), years	46 (19–75)	45 (20–78)
≥65 years, n (%)	25 (3)	8 (2)
Male, n (%)	623 (82)	313 (83)
Race, n (%)		
White	573 (75)	282 (75)
Black	155 (20)	82 (22)
Asian/Other	35 (5)	14 (4)
Region, n (%)		
North America	358 (47)	202 (53)
Europe	405 (53)	176 (47)
CD4+ count, median (IQR), cells/μL	630 (468-806)	624 (466-795)
WHO clinical stage 4 HIV-1 infection, n (%)	79 (10)	36 (10)
eGFR (Cockcroft-Gault), median (IQR), mL/min	104.2 (86.9-122.5)	103.3 (86.3-122.4)
Previous use of ≥5 ARVs, n (%)	447 (59)	217 (57)
≥2 PIs	318 (42)	154 (41)
≥3 NRTIs	328 (43)	146 (39)
≥1 NNRTI	225 (29)	115 (30)
≥1 INSTI	39 (5)	24 (6)
Prior VF, n (%)	116 (15)	53 (14)
PI	51 (7)	29 (8)

Demographics	SYMTUZA (N=763)	bPI (N=378)
NRTI	90 (12)	40 (11)
NNRTI	50 (7)	24 (6)
INSTI	7 (1)	3 (1)
bPI at screening, n (%)		
DRV	537 (70)	266 (70)
DRV/r	439 (58)	202 (53)
DRV/COBI	98 (13)	64 (17)
ATV	167 (22)	82 (22)
ATV/r	161 (21)	81 (21)
ATV/COBI	6 (1)	1 (<1)
LPV	59 (8)	30 (8)
Abbreviations: ARV, antiretroviral; ATV, atazanavir; bPI, boosted protease inhibitor; COBI, cobicistat; DRV, darunavir; eGFR, estimated glomerular filtration rate; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LPV, lopinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; VF, virologic failure.		

Efficacy

- Efficacy outcomes at weeks 48 and 96 are summarized in Table: Efficacy Outcomes at Weeks 48 and 96 in the SYMTUZA Arm (ITT Population).
- At week 48, the proportion of patients with confirmed virologic rebound was 2.5% (n=19) for SYMTUZA and 2.1% (n=8) for the bPI group, demonstrating non-inferiority (difference 0.4%; 95% CI: −1.5% to 2.2%).[1]
    - Most rebounders (12/19 SYMTUZA and 4/8 bPI) were resuppressed by week 48.
    - There were 3 rebounders with confirmed VL ≥200 copies/mL in the SYMTUZA group.
    - Noninferiority was confirmed in the per-protocol analysis (1.9% [n=14] vs 0.8% [n=3]; difference 1.1%; 95% CI -0.3% to +2.5%).
    - Results were consistent across patient subgroups (gender, race, and age).[3]
    - Number of prior ARVs used did not impact the efficacy of SYMTUZA.[3]
- Virologic response rates at week 48 were 94.9% and 93.7% in the SYMTUZA and bPI groups, respectively (difference 1.2%, 95% CI: −1.7% to 4.1%).[1]
    - Virologic rebound and response rates were consistent across subgroups based on bPI and boosting agent used at baseline.[3]
- VF (VL ≥50 copies/mL in week 48 window or discontinued with last VL ≥50 copies/mL) occurred in 6 (0.8%) SYMTUZA patients and 2 (0.5%) bPI patients.[1]
- The proportion of patients with no virologic data at the week 48 window were 4.3% in the SYMTUZA arm and 5.8% in the bPI arm.
- PDVR (VL ≥50 copies/mL) cumulative through week 96 was consistent using the per-protocol analysis.[2]
- Through 96 weeks, no patient in the SYMTUZA arm discontinued due to loss of virologic efficacy.
    - Virologic responses were consistent with the per-protocol <50 copies/mL FDA snapshot analysis.
    - PDVR and FDA-snapshot outcomes were consistent across baseline patient subgroups: sex, age, race, previous ARV use, previous VF, screening bPI, and screening boosting agent.
- In a post hoc analysis, no difference in virologic suppression was observed between patients with or without baseline neurologic and/or psychiatric comorbidities (NPCs) at week 96 (91% vs 91% of patients, respectively, achieved VL <50 copies/mL per the ITT-FDA snapshot analysis).[6]
- In the SYMTUZA arm, of the 116 patients with ≥1 previous 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.

- The least squares mean (LSM) increases from baseline in CD4+ count at week 48 were 18.7 (95% CI: 4.5-32.9) cells/μL in the SYMTUZA group vs 4.9 (95% CI: -12.9 to 22.7) cells/μL in the bPI group.
- The LSM (95% CI) increase from baseline in CD4+ cell count to week 96 was 32.1 (95% CI: 16.4-47.8) cells/mm^3 in the SYMTUZA 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.
- Median cumulative adherence via pill count through week 48: 99.7% SYMTUZA vs 99.3% bPI.

Efficacy Outcomes at Weeks 48 and 96 in the SYMTUZA Arm (ITT Population)[2]

Outcome	SYMTUZA Arm (N=763)		Late Switch Arm (N=352)
	Baseline - Week 48	Baseline - Week 96	Switch – Week 96
PDVR			
≥50 copies/mL, n (%)	19 (2.5)	24 (3.1)	8 (2.3)
Rebounders resuppressed at end of period, n/N	12/19	14/24	2/8
≥200 copies/mL, n (%)	3 (0.4)	4 (0.5)	2 (0.6)
Rebounders resuppressed at end of period, n/N	0/3	2/4	2/2
FDA snapshot			
VL <50 copies/mL, n (%)			
VL <50 copies/mL	724 (94.9)	692 (90.7)	330 (93.8)
VL ≥50 copies/mL	6 (0.8)	9 (1.2)	6 (1.7)
No virologic data	33 (4.3)	62 (8.1)	16 (4.5)
VL <200 copies/mL, n (%)			
VL <200 copies/mL	725 (95.0)	696 (91.2)	336 (95.5)
VL ≥200 copies/mL	3 (0.4)	2 (0.3)	0
No virologic data	35 (4.6)	65 (8.5)	16 (4.5)

Abbreviations: FDA, Food and Drug Administration; ITT, intention to treat; PDVR, protocol-defined virologic rebound; VL, viral load.

Resistance

- Overall, of the 140 patients with previous VF and geno-archive data, 6 (4%) had DRV RAMs, 5 (4%) had tenofovir (TFV) RAMs, and 53 (38%) had FTC RAMs, mainly at reverse transcriptase position 184 (Table: Prevalence of Baseline RAMs in HIV-1 Proviral DNA from Patients with Previous VF in EMERALD).[5]
  - Genotypic susceptibility data showed 61% were susceptible to all NNRTIs, 51% to all NRTIs, 83% to all PIs (100% to DRV) and 89% to all INSTIs.
  - All of these patients with DRV, FTC, and TFV RAMs had VL <50 copies/mL at week 48 or at the last on-treatment VL.

Prevalence of Baseline RAMs in HIV-1 Proviral DNA from Patients with Previous VF and Geno-archive Data in EMERALD[5]

Genotypic susceptibility	SYMTUZA (n=98)	bPI (n=42)	Total (N=140)
≥1 DRV RAMs[a], n (%)	4[b] (4)	2 (5)	6 (4)
L33L/F	0	1 (2)	1 (1)
T74T/P	0	1 (2)	1 (1)
L76L/V	1 (1)	0	1 (1)
I84I/V	4 (4)	0	4 (3)
≥1 primary PI RAMs[a], n (%)	20 (20)	7 (17)	27 (19)
D30D/N	4 (4)	0	4 (3)
M46M/I/L	8 (8)	5 (12)	13 (9)

I50I/L	0	1 (2)	1 (1)
Q58Q/E	0	1 (2)	1 (1)
T74T/P	0	1 (2)	1 (1)
L76L/V	1 (1)	0	1 (1)
V82V/A/T	1 (1)	2 (5)	3 (2)
I84I/V	4 (4)	0	4 (3)
N88N/S	2 (2)	0	2 (1)
L90L/I/M	8 (8)	3 (7)	11 (8)
≥1 NRTI RAMs, n (%)	46 (47)	23 (55)	69 (49)
≥1 TFV RAMs[a], n (%)	4 (4)	1 (2)	5 (4)
K65K/R	4 (4)	0	4 (3)
K70K/D/E/N	0	1 (2)	1 (1)
≥1 TAMs[a,c], n (%)	34 (35)	14 (33)	48 (34)
M41M/L	18 (18)	8 (19)	26 (19)
D67D/N	10 (10)	7 (17)	17 (12)
K70K/R	18 (18)	6 (14)	24 (17)
L210L/W	9 (9)	3 (7)	12 (9)
T215A/C/D/E/F/G/I/L/N/S/T/Y	20 (20)	12 (29)	32 (23)
K219K/E/Q	11 (11)	4 (10)	15 (11)
≥1 FTC RAMs[a], n (%)	35 (36)	18 (43)	53 (38)
K65K/R	4 (4)	0	4 (3)
M184M/I/V	31 (32)	18 (43)	49 (35)
≥1 NNRTI RAMs, n (%)	44 (45)	14 (33)	58 (41)
V90V/I	5 (5)	3 (7)	8 (6)
A98A/G/S	5 (5)	1 (2)	6 (4)
L100L/I	2 (2)	0	2 (1)
K101K/E/P/Q/T	7 (7)	1 (2)	8 (6)
K103K/N/R/S	19 (19)	6 (14)	25 (18)
V106V/A/I	3 (3)	1 (2)	4 (3)
V108V/I/M	6 (6)	1 (2)	7 (5)
E138E/A/G/K/P/Q/R	13 (13)	1 (2)	14 (10)
V179V/A/F/I/T	2 (2)	0	2 (1)
Y181Y/C	8 (8)	3 (7)	11 (8)
Y188Y/H/L	3 (3)	0	3 (2)
G190G/A/R/S	8 (8)	4 (10)	12 (9)
H221H/Y	1 (1)	1 (2)	2 (1)
P225P/H	1 (1)	1 (2)	2 (1)
M230M/L	0	1 (2)	1 (1)
≥1 primary INSTI RAMs, n (%)	5 (5)	1 (2)	6 (4)
T66T/I	2 (2)	0	2 (1)
Q148Q/H/R	1 (1)	1 (2)	2 (1)
N155N/H	2 (2)	0	2 (1)

Abbreviations: bPI, boosted protease inhibitor; DRV, darunavir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance associated mutation; TAM, thymidine analogue-associated mutation; TFV, tenofovir; VF, virologic failure.
[a]Observed mutations were concatenated.
[b]In one patient, 2 DRV RAMs were observed (I84I/V and L76L/V).
[c]TAMs: M41L, D67N, K70R, L210W, T215Y/F, K291Q/E.

- Through week 96, there were 24/763 (3%) patients in the SYMTUZA arm and 8/352 (2%) patients in the control arm who had PDVR.[7]
  - Of the 24 SYMTUZA patients with PDVR, 22 had baseline geno-archive data and none had archived RAMs to DRV, FTC, or TFV; additionally, no primary PI RAMs nor thymidine analogue-associated mutations (TAMs) were observed.
  - Post-baseline genotypic data was available for 4 rebounders in the SYMTUZA arm and 2 rebounders in the control arm.
    - No DRV, primary PI, TFV, or FTC RAMs were observed, and all patients had HIV-1 virus susceptible to all drugs in the regimens.

Safety

- Safety data through 96 weeks is reported in Table: Overview of Treatment-Emergent AEs and Laboratory Abnormalities and Median (IQR) Change from Baseline in Lipids at Week 96.[2]
  - The incidence of AEs in the SYMTUZA arm was similar in the overall population and in the subgroups of age, gender, race, screening bPI, and screening boosting agent.[4]
  - Through week 96, most AEs, regardless of causality, were grade 1 or 2.[2]
  - Most treatment-emergent laboratory abnormality events were grade 1 or 2 through week 96.
  - The most common grade 3 AE in the SYMTUZA arm was increased low-density lipoprotein (LDL) cholesterol, which was reported for 2 patients before week 48 and 2 patients after week 48 (both <1%).
  - Grade 3 AEs occurring in the late switch arm from week 52 through week 96 were pneumonia, tendon rupture, hypercholesterolemia, and depression, each reported in 2 patients (<1%).
  - Three cases of myocardial infarction (0.3%, 3/1080) occurred after week 48 – 2 in the SYMTUZA arm and 1 in the late switch arm.
  - In the SYMTUZA arm, similar median increases from baseline to week 96 were observed in fasting total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and total cholesterol/HDL-C ratio in the overall population and across the subgroups of age, gender, and race.[4]
  - During treatment, lipid-lowering drugs were started by 4% (32/763) and 8% (59/763) of patients by weeks 48 and 96, respectively, in the SYMTUZA arm, and by 3% (11/378) and 5% (19/352), respectively, in the control arm.[2]

Overview of Treatment-Emergent AEs and Laboratory Abnormalities and Median (IQR) Change from Baseline in Lipids at Week 96[2]

	SYMTUZA Arm				Late Switch Arm		
	SYMTUZA (Baseline -Week 48) (N=763)	**SYMTUZA (Week 48 – Week 96) (N=728)**	**SYMTUZA (Baseline -Week 96) (N=763)**	***P*-value[a,b]**	**bPI + FTC/TDF (Baseline – Week 52) (N=378)**	**SYMTUZA[c] (Week 52 – Week 96) (N=352)**	***P*-value[a,b]**
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% SYMTUZA arm through 96 weeks), n (%)							
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% in 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), n/N (%)							
Fasting LDL-cholesterol (≥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							
Total cholesterol, mg/dL	+19.9 (1.2 to 39.4)	ND	+22.0 (-0.4 to 44.0)	<0.001	+1.3 (-12.0 to 20.0)	+22.0 (3.0 to 42.7)	<0.001
HDL cholesterol, mg/dL	+2.7 (-3.0 to 8.0)	ND	+3.0 (-2.0 to 8.5)	<0.001	0.0 (-4.6 to 4.0)	+3.3 (-2.0 to 8.0)	<0.001
LDL cholesterol, mg/dL	+15.9 (0.0 to 32.0)	ND	+17.0 (-3.0 to 35.2)	<0.001	+1.9 (-12.0 to 17.0)	+15.0 (0.0 to 32.9)	<0.001
Triglycerides, mg/dL	+5.7 (-21.0 to 39.0)	ND	+7.0 (-25.0 to 43.0)	<0.001	+4.9 (-23.0 to 39.0)	+8.0 (-25.8 to 47.0)	0.004
Total cholesterol/HDL cholesterol ratio	+0.20 (-0.20 to 0.60)	ND	+0.20 (-0.40 to 0.70)	<0.001	+0.10 (-0.30 to 0.40)	+0.20 (-0.30 to 0.70)	<0.001

Abbreviations: AE, adverse event; BMD, bone mineral density; bPI, boosted protease inhibitor; eGFR, estimated glomerular filtration rate; FTC/TDF, tenofovir disoproxil fumarate/emtricitabine; IQR, interquartile range; ND, not determined.

[a]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).

[b]Reference for the SYMTUZA arm is study baseline and for the late switchers is the last value before the switch.

[c]Comprising 44 weeks of SYMTUZA exposure (ie, from the switch to SYMTUZA at week 52).

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

[e]SYMTUZA arm: abdominal pain, diarrhea, gastroesophageal 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 1 patient prior to week 48 and chronic kidney disease in a patient after week 48); SYMTUZA 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.

Renal Safety

- No renal AEs suggested treatment-emergent proximal renal tubulopathy through week 96.

- At week 48, increases in serum creatinine were larger for SYMTUZA vs bPI (1.3 μmol/L vs 0.6 μmol/L; not significant).
    - However, in patients switching from DRV/COBI to SYMTUZA, serum creatinine decreased and eGFR increased (data not provided).
- Switching to SYMTUZA resulted in significant improvement in glomerular proteinuria and proximal tubular proteins at week 48 ($P<0.001$).
    - Proteinuria markers continued to improve through week 96 and similar results were observed across the subgroups of age, gender, and race.[4]
- In the SYMTUZA arm, improvements in renal biomarkers seen at 48 weeks compared with baseline were maintained through week 96.
- In the SYMTUZA arm, the median changes in eGFR based on cystatin C were stable (range: -2 to +2 mL/min/1.73m^2) through week 96 across the subgroups of age, gender, race, screening bPI, and screening boosting agent.[4]

Bone Safety

- At week 48, in the bone substudy, there were significant differences in the mean change from baseline in bone mineral density in the SYMTUZA group (n=209) as compared to the bPI group (n=108).
    - Hip: +1.43% SYMTUZA vs -0.26% bPI; $P<0.001$.
    - Lumbar spine: +1.49% SYMTUZA vs -0.63% bPI; $P<0.001$
    - Femoral neck: +0.66% SYMTUZA vs -0.54% bPI; $P=0.004$
- The percentage of patients with ≥3% increase in BMD at week 48 was 20.2% vs 4.1% for hip, 31.8% vs 8.9% for spine, and 22.9% vs 11.3% for femoral neck in the SYMTUZA and bPI groups, respectively.
- Changes from baseline in bone biomarker levels were significantly different between the two arms at week 48, indicating less bone turnover for SYMTUZA vs bPI.
- At week 48, improvements in renal function and BMD were observed regardless of age, gender, or race.[3]
- Over 96 weeks, there were sustained improvements in BMD at the hip (+1.85% at week 96 vs baseline), lumbar spine (+2.00%), and femoral neck (+1.38%) in the SYMTUZA arm (all $P<0.001$ vs baseline, paired t-test).
    - Numerical increases in BMD of the hip, lumbar spine, and femoral neck were also observed across the demographic subgroups of age, gender, and race.[4]
- Similar significant improvements in BMD at week 96 compared with the value prior to switching were seen in the late switch arm.
- In the SYMTUZA arm, the proportion of patients who had a ≥3% decrease in hip, lumbar spine, and femoral neck BMD at week 96 vs baseline was stable through week 96.
- In the late switch arm, more patients had a ≥3% increase in BMD at each site over 44 weeks of SYMTUZA treatment than over the first 48 weeks of bPI + TDF/FDC therapy, and fewer patients had a ≥3% decrease in BMD.
- Changes in bone biomarkers over weeks 52-96 in the late switch arm were similar to those reported by week 48 in the SYMTUZA arm.

Neurologic/Psychiatric Adverse Effects

- In post hoc analysis, patients with (n=294) vs. without (n=469) baseline NPCs reported a higher incidence of neurologic and psychiatric AEs; however, the incidence of drug-related AEs did not differ between groups.[6]

Gastrointestinal Adverse Effects

- In post hoc analysis, the incidences of SYMTUZA-related GI AEs of interest were low, tended to present within the first weeks of therapy, and rapidly decreased thereafter.[8]
  - The incidence of SYMTUZA-related diarrhea and nausea was 2% and <1%, respectively, during week 1 and decreased to ≤0.1% after week 2.
  - The prevalence of SYMTUZA-related diarrhea and nausea was each <1% starting at week 2.
  - One case of SYMTUZA-related abdominal discomfort was reported (week 1), and the incidence of SYMTUZA-related flatulence was 0.4% at week 1 and <0.1% thereafter.

LITERATURE SEARCH

- A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 25 October 2023.

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