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

Study Overview[a]

AMBER

Phase 3, randomized, active-controlled, double-blind, **noninferiority study**

Evaluated the efficacy and safety of single-tablet regimen of **D/C/F/TAF vs D/C+F/TDF**

in **antiretroviral treatment-naïve** HIV-1-infected **adults**

N=725

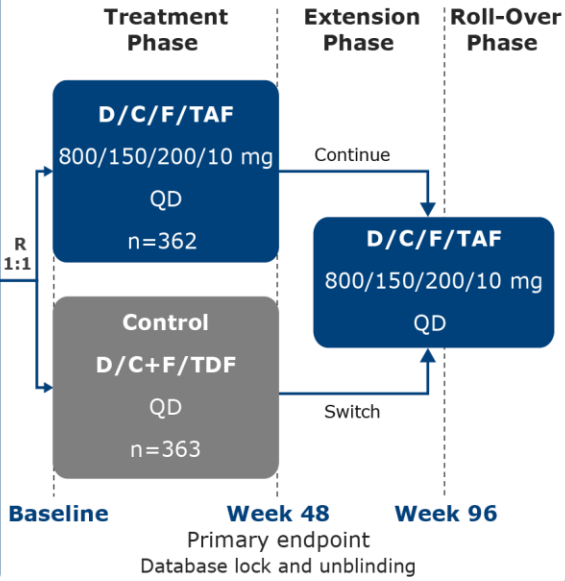
Study Design[a,b]

Key Inclusion Criteria

- Treatment-naïve adults (≥18 years of age)
- VL ≥1000 copies/mL
- CD4+ >50 cells/mm^3
- eGFR$_{cr}$ ≥70 mL/min
- Genotypic sensitivity to D, F, and TFV

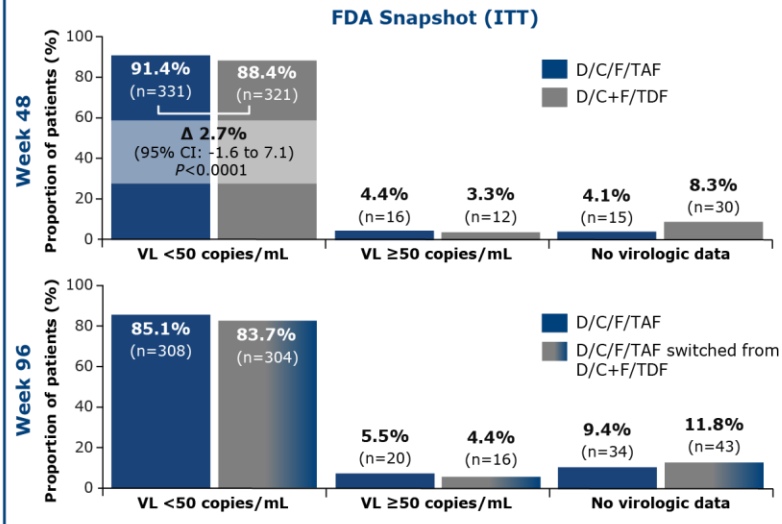
Key Exclusion Criteria

- New AIDS-defining condition ≤30 days prior to screening
- Clinically significant disease (eg, malignancy, severe infections)
- Hepatitis B or C coinfection



Efficacy[a,b]

- **Primary endpoint**: Noninferiority of **D/C/F/TAF vs D/C+F/TDF** for VL <50 copies/mL **(virologic suppression)** at week 48 was met[a]



- At week 96, ITT FDA-snapshot outcomes (VL <50 and ≥50 copies/mL) were consistent across age, gender, and race subgroups[b]

Safety and Tolerability[b]

- **Most common AEs regardless of causality through 96 weeks** (≥10% D/C/F/TAF group) were:
  - diarrhea (23%)
  - nasopharyngitis (16%)
  - headache (15%)
- **Grade 3 or 4 fasting LDL-C level** (≥190 mg/dL) was observed in 9% of patients in the D/C/F/TAF group vs 4% in the control group after the switch
- **AE-related discontinuations** in the D/C/F/TAF group were 3% through week 96
- No study drug-related discontinuations **due to renal AEs** in either treatment groups
- In the D/C/F/TAF group, there was no change in hip **BMD**, with a decrease in lumbar spine and femoral neck BMD through week 96 (mean percentage change from baseline -0.3% [*P*=0.47], -0.9% [*P*=0.04], and -1.3% [*P*=0.005], respectively)

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

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; BMD, bone mineral density; CD4, cluster of differentiation 4; CI, confidence interval; D/C, darunavir/cobicistat; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; eGFR$_{cr}$, estimated glomerular filtration rate based on serum creatinine; FDA, Food and Drug Administration; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; QD, once daily; R, randomization; TFV, tenofovir; VL, viral load.

[a]Eron (2018). [b]Orkin (2020).

SUMMARY

- The AMBER study is a phase 3, randomized, active-controlled, double-blind noninferiority study to evaluate the efficacy and safety of SYMTUZA vs darunavir (DRV)/cobicistat (COBI) fixed dose combination co-administered with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in antiretroviral treatment-naïve human immunodeficiency virus type 1 (HIV-1)-infected adults.[1,2]
- At week 48, in the intention to treat (ITT) population, viral suppression (viral load [VL] <50 copies/mL) was achieved in 91.4% of patients in the SYMTUZA arm compared with 88.4% of patients in the control arm.[1]
- At week 96, in the ITT population, VL <50 copies/mL was achieved in 85.1% of patients in the SYMTUZA arm.[2]
- Efficacy and safety results through week 96 in the subgroups of age, gender, race, baseline VL, baseline CD4$^+$ cell count, and WHO clinical stage were consistent with the overall population.[3]

CLINICAL DATA

AMBER STUDY

The AMBER study is a phase 3, randomized, active-controlled, double-blind noninferiority study to evaluate the efficacy and safety of SYMTUZA vs DRV/COBI fixed dose combination co-administered with TDF/FTC in antiretroviral treatment-naïve HIV-1-infected adults (N=725).[1,2]

Study Design/Methods

- Select inclusion criteria: Viral load (VL) ≥1000 copies/mL; CD4+ >50 cells/mm^3; estimated glomerular filtration rate based on serum creatinine ($eGFR_{cr}$) ≥70 mL/min.[1]
- Patients who were hepatitis B or C positive, pregnant, or had cirrhosis were ineligible.[1,4]
- Patients were stratified by screening VL (< / ≥100,000) and by screening CD4+ cell counts (< / ≥200 cells/mm^3) and then randomized to a single-tablet regimen (STR) consisting of SYMTUZA (darunavir 800 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg) with matching DRV/COBI +TDF/FTC placebo or the active-control regimen of DRV/COBI +TDF/FTC with a matching SYMTUZA placebo.[1]
- After database lock and unblinding for the week 48 analysis, patients randomized to SYMTUZA could continue on SYMTUZA and patients randomized to the DRV/COBI +TDF/FTC control arm could switch to SYMTUZA in an open-label, single arm extension phase (late switch) until week 96.[2]
- Primary endpoint: VL <50 copies/mL (Food and Drug Administration [FDA] Snapshot) at week 48 (non-inferiority margin set at 10%).[1]
- Secondary endpoints: VL <50 copies/mL at week 96 (FDA Snapshot); VL <200 copies/mL and ≥200 copies/mL (FDA Snapshot); VL <50 copies/mL via time-to-loss of virologic response algorithm at weeks 48 and 96; change from baseline in CD4+ count, serum creatinine (SCr), estimated glomerular filtration rate (eGFR), and renal biomarkers at weeks 48 and 96; change from baseline in hip/spine bone mineral density (BMD) at weeks 48 and 96; grade 3-4 adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuations up to week 96; development of resistance in virologic failures (VFs).[4]
- Subgroup analyses for efficacy and safety through week 96 included baseline demographics and characteristics of age (≤50 vs >50 years), gender, race (non-Black/African American vs Black/African American), VL ≤100,000 vs >100,000 copies/mL, CD4$^+$ cell count <200 vs ≥200 cells/mm^3, WHO clinical stage of HIV infection (asymptomatic vs mild symptoms), and HIV-1 subtype (B vs non-B).[3]
- Genotypic resistance testing was performed using GenoSure® MG at screening.[1]
- PhenoSense® GT was used for genotypic and phenotypic testing post-baseline in patients with protocol-defined VF (PDVF; VL ≥50 copies/mL) with VL ≥400 copies/mL.[1] Deep sequencing was performed post-hoc using NGS GenoSure® MG.[2]

- Adherence was determined by drug accountability based on pill count cumulative from baseline to switch and from switch to week 96 for patients who returned all dispensed bottles.[2]

Results

Baseline Characteristics and Patient Disposition

- A total of 725 patients (n=362 SYMTUZA, n=363 control) were randomized and included in the intention-to-treat (ITT) population.[1]
- Of these patients through 48 weeks, 93.6% (339/362) in the SYMTUZA group and 92.3% (335/363) in the control group completed therapy.[1]
    - The most common reasons for discontinuing the study were AEs, withdrawn consent, and loss to follow-up.

Baseline Characteristics[1]

	SYMTUZA (n=362)	Control (n=363)	Total (N=725)
Age, median (IQR), years	34 (27–42)	34 (27–42)	34 (27-42)
Age >50 years, n (%)	36 (10)	32 (9)	68 (9)
Gender, n (%)			
Female	44 (12)	41 (11)	85 (12)
Male	318 (88)	322 (89)	640 (88)
Race, n (%)			
White	300 (83)	300 (83)	600 (83)
Black/African American	40 (11)	40 (11)	80 (11)
Other races	22 (6)	23 (6)	45 (6)
Ethnicity, n (%)			
Hispanic or Latino	50 (14)	45 (12)	95 (13)
Time since diagnosis, median (IQR), months	5.73 (2.53-25.59)	4.30 (2.07-17.74)	4.83 (2.33-21.62)
Viral load, median (IQR), $\log_{10}$ copies/mL	4.44 (4.03–4.82)	4.57 (4.15–4.88)	4.52 (4.10-4.87)
Viral load ≥100,000 copies/mL, n (%)	60 (17)	70 (19)	130 (18)
CD4+ count, median (IQR), cells/mm^3	461.5 (342-617)	440.0 (325-594)	453.0 (333-601)
CD4+ cell count <200 cells per mm^3, n (%)	22 (6)	29 (8)	51 (7)
$eGFR_{cr}$, median (IQR), mL/min (Cockcroft-Gault)	119.3 (104.8–135.2)	118.4 (103.2–138.4)	119.1 (104.4-136.5)
Genotype[a] at screening, n (%)	N = 361[b]	N = 362[b]	N=723
≥1 darunavir RAMs	3 (1)	4 (1)	7 (1)[c]
≥1 primary PI RAMs	7 (2)	8 (2)	15 (2)
≥1 NRTI RAMs	18 (5)	16 (4)	34 (5)[d]
≥1 NNRTI RAMs	55 (15)	63 (17)	118 (16)[e]

Abbreviations: CD4, cluster of differentiation 4; $eGFR_{cr}$, estimated glomerular filtration rate based on serum creatinine; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAMs, resistance-associated mutations.
[a]GenoSureMG.
[b]One patient in each group had failed screening genotypes and were enrolled based on local genotypes.
[c]Six V11I, one L33F.
[d]The most prevalent NRTI mutation: A62V: 21/725 (2.9%).
[e]The most prevalent NNRTI mutation: K103N: 26/725 (3.6%).

- A total of 335 patients in the SYMTUZA arm continued on SYMTUZA in the extension phase after week 48.[2]
    - Sixteen patients (5%) discontinued between weeks 48-96 (5 withdrew consent, 4 lost to follow-up, 4 physician decision, and 3 other reasons).
    - A total of 319 patients in the SYMTUZA arm reached week 96.

- A total of 295 patients in the control arm switched to SYMTUZA after week 48.[2]
  - Five patients (2%) discontinued between weeks 48-96 (1 due to AEs, 1 withdrew consent, 2 lost to follow-up, 1 other reasons).
  - A total of 290 patients reached week 96 with 7/290 completing the study and 283/290 ongoing.

Efficacy

- At week 48, in the ITT population, viral suppression (VL <50 copies/mL; FDA snapshot analysis) was achieved in 331 patients (91.4%) in the SYMTUZA arm compared with 321 patients (88.4%) in the control arm (difference 2.7%; 95% confidence interval [CI]: -1.6 to 7.1; *P*<0.0001). (Table: Proportion of Patients with Virologic Response at 48 Weeks, FDA Snapshot [ITT]).[1]
  - There were no differences observed in virologic response between various subgroups (gender, race, age, baseline VL, baseline CD4+, World Health Organization clinical staging).[1,5]

Proportion of Patients with Virologic Response at 48 Weeks, FDA Snapshot (ITT)[1]

Outcomes	SYMTUZA (n=362)	Control (n=363)	Percentage difference (95% CI)[a]
Virologic success[b]			
VL <50 copies/mL, n (%)	331 (91.4)	321 (88.4)	2.7 (-1.6 to 7.1)
VL ≥50 copies/mL, n (%)	16 (4.4)	12 (3.3)	
Last VL in week 48 window ≥50 copies/mL	9 (2.5)	9 (2.5)	
Discontinued for efficacy reasons	1 (0.3)[c]	0	
Discontinued due to other reasons than efficacy, AEs, or death and last available VL ≥50 copies/mL[d]	6 (1.7)	3 (0.8)	
No VL data in week 48 window, n (%)	15 (4.1)	30 (8.3)	
Discontinued due to AE/death	8 (2.2)	16 (4.4)	
Discontinued due to other reasons and last available VL <50 copies/mL (or missing)[e]	4 (1.1)	9 (2.5)	
Missing data during window but on study drug	3 (0.8)	5 (1.4)	

Abbreviations: AEs, adverse events; CD4, cluster of differentiation 4; CI, confidence interval; ITT, intention-to-treat; VL, viral load.
[a]Calculated with the Mantel-Haenszel test adjusting for screening VL (≤ or >100,000 copies/mL) and CD4+ count (< or ≥200 cells/mm^3).
[b]For the ITT FDA-snapshot analysis at week 48, the last available VL value in the week-48 time-point window was used to determine response.
[c]Patient reached a virologic endpoint per investigator's assessment. The patient had a VL at week 36 of 168 copies/mL and was withdrawn by the investigator. The patient's last VL on-treatment (at the early study treatment discontinuation visit 16 days post-week 36) was 31 copies/mL.
[d]Lost to follow-up (4 vs 2 patients), withdrawal by 1 patient (1 vs 1), and other reasons (1 vs 0).
[e]Lost to follow-up (0 vs 3), physician decision (2 vs 0), withdrawal by patient (1 vs 5), and other reasons (1 vs 1).

- At week 96, in the ITT population, viral suppression (VL <50 copies/mL; FDA snapshot analysis) was achieved in 308 patients (85.1%) in the SYMTUZA arm compared with 304 patients (83.7%) in the control arm. (Table: Proportion of Patients with Virologic Response at 96 Weeks, FDA Snapshot [ITT]).[2]
  - Results were consistent across patient subgroups (baseline VL, baseline CD4+ count, WHO clinical stage of HIV infection [asymptomatic vs mild symptoms], HIV-1 subtype [B vs non-B], age, gender, and race).[3]
- In a post hoc analysis, 80% of patients (70/88) with baseline neurologic and/or psychiatric comorbidities (NPCs) and 87% of patients (238/274) without baseline NPCs achieved viral suppression (VL <50 copies/mL; ITT-FDA snapshot analysis) at week 96 of SYMTUZA treatment.[6]

Proportion of Patients with Virologic Response at 96 Weeks, FDA Snapshot (ITT)[2]

Outcomes	SYMTUZA (n=362)	Control (n=363)
Virologic Response[a], n (%)		
VL <50 copies/mL	308 (85.1)	304 (83.7)
VL ≥50 copies/mL	20 (5.5)	16 (4.4)
Last VL in week 96 window ≥50 copies/mL	6 (1.7)	9 (2.5)
Discontinued for efficacy reasons[b]	5 (1.4)	2 (0.6)
Discontinued due to other reasons than efficacy, AEs or death and last available VL≥50 copies/mL	9 (2.5)	5 (1.4)
No virologic data	34 (9.4)	43 (11.8)
Discontinued due to AE/death	8 (2.2)	18 (5.0)
Discontinued due to other reasons and last available VL <50 copies/mL (or missing)	21 (5.8)	21 (5.8)
Missing data during window but on study drug	5 (1.4)	4 (1.1)
VL <200 copies/mL	312 (86.2)	312 (86)
VL ≥200 copies/mL	15 (4.1)	6 (1.7)
Last VL in week 96 window ≥200 copies/mL	2 (0.6)	1 (0.3)
Discontinued for efficacy reasons[b]	5 (1.4)	2 (0.6)
Discontinued due to other reasons than efficacy, AEs or death and last available VL≥200 copies/mL	8 (2.2)	3 (0.8)
No virologic data	35 (9.7)	45 (12.4)
Discontinued due to AE/death	8 (2.2)	18 (5.0)
Discontinued due to other reasons and last available VL <200 copies/mL (or missing)	22 (6.1)	23 (6.3)
Missing data during window but on study drug	5 (1.4)	4 (1.1)

Abbreviations: ITT, intention-to-treat; VL, viral load.
[a]Last available VL value in the week 96 time point window was used to determine response.
[b] Five patients in the SYMTUZA arm discontinued from the study due to efficacy-related reasons per investigator's assessment (physician decision), of which three had last on treatment VL <50 copies/ml, and two patients in the control arm (one physician decision [during DRV/COBI +TDF/FTC treatment] and one other [during SYMTUZA treatment]), of which one had last on-treatment VL <50 copies/ml.

Resistance

- As depicted by the protocol, at screening, all enrolled patients demonstrated genotypic sensitivity to DRV, FTC, and tenofovir (TFV) based on a genotype report.[1]
  - A total of 1% (n=7) of patients had viruses with ≥1 DRV resistance-associated mutation (RAM) and 2% (n=15) of patients had primary protease inhibitor (PI) RAMs.
  - No RAMs related to FTC or TFV were detected.
  - Nonnucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitor (NRTI) RAMs were detected in 16% (n=118) and 5% (n=34) of patients, respectively.
- Through week 48, there were 8 patients in the SYMTUZA arm and 6 patients in the control arm who had PDVF, with paired screening and post-baseline on-treatment genotypes available for 7 and 2 patients, respectively.[1]
  - In 1 patient in the SYMTUZA arm, the NRTI RAM M184I/V, conferring phenotypic resistance to FTC and lamivudine, was detected at week 36.[7]
    - At week 12, only the wild-type genotype was detected.[7]
    - At week 36, M184I (32%) and M184V (67%) were detected.[7]
    - M184V was detected pre-treatment at screening by deep sequencing as a minority variant (9%).[1]
    - The patient also had K103N at screening, indicating transmitted NNRTI (efavirenz/nevirapine) resistance.[1]
    - Although adherence based on pill count was ≥95%, D serum concentrations were low, and the patient discontinued the study due to noncompliance.[1]

- Through week 96, a total of 15/362 (4%) patients in the SYMTUZA arm and 19/363 (5%) patients in the control arm (pre- and post-switch) had PDVF, with paired screening and post-baseline on-treatment genotypes available for 9 and 8 patients, respectively.[8]
    - There was no development of DRV, primary PI, or TFV RAMs in either arm.
    - In 1 patient in the control arm, M184V (deep sequencing codon variant of 99%) was detected at week 84 after switch to SYMTUZA.
        - M184V was not detected pre-treatment via deep sequencing.
        - Adherence for this patient based on pill count was 90% prior to switching and 80% after switching; no pharmacokinetic data were available.

Adherence

- Through week 48, adherence rates exceeded 80% in both arms (see Table: Drug Accountability Through Week 96 In The AMBER Phase 3 Clinical Study).[9]
- After week 48, when the study was unblinded, the matching placebos were discontinued, and all patients went from 3 tablets per day to 1 tablet (SYMTUZA STR) per day, adherence improved.[9]
    - In the SYMTUZA group, the proportion of patients with adherence >95% increased from 87% at week 48 to 90% at week 96 (*P*=not significant).
    - In the control group, the proportion of patients with adherence >95% improved from 83% at week 48 to 90% at week 96 (*P*=0.0046).

Drug Accountability[a] Through Week 96 In the AMBER Phase 3 Clinical Study[9]

Treatment Adherence[b]	SYMTUZA (N=362)		Control (N=363)	
	BL-SW	SW-Week 96	BL-SW	SW-Week 96
N	289	259	282	250
>95%, n (%)	252 (87)	233 (90)	233 (83)	225 (90)
>80%-≤95%, n (%)	34 (12)	23(9)	47 (17)	20 (8)
>65%-≤80%, n (%)	1 (<1)	3 (1)	1 (<1)	5 (2)
≤65%, n (%)	2 (1)	0	1 (<1)	0
Median (IQR), %	99.6 (97.9;100.0)	100.0 (98.4;100.6)	99.7 (97.4;100.0)	100.0 (98.3;100.6)
P-value[c]		0.3449		0.0046

Abbreviations: BL, baseline; IQR, interquartile range; SW, switch to SYMTUZA.
[a]Derivation: cumulative treatment adherence (based on pill count) in patients who returned all dispensed bottles prior to or at the week 96 visit.
[b]Based on the worst adherence to any of the antiretrovirals in the regimen.
[c]*P*-value from McNemar's Exact Test comparing within treatment arm adherence (>95% vs ≤95%) during baseline to switch and SYMTUZA during switch to week 96 (performed post-hoc in EMERALD).

Safety

- Safety data through 48 weeks is reported in Table: Treatment-Emergent Adverse Events and Laboratory Abnormalities Through 48 Weeks.[1]
    - Through week 48, laboratory abnormalities were mostly grade 1 or 2.
    - There were 6 (1.7%) patients in the SYMTUZA arm that started lipid lowering therapy compared with 2 patients (0.6%) in the control arm through week 48.
    - There were no deaths reported in either study arm during the 48-week treatment phase.
    - Through week 48, 1 patient in the control group died following grade 4 sepsis in the follow-up phase (11 days after last study drug intake), which was not considered related to study drug.

Treatment-Emergent Adverse Events and Laboratory Abnormalities Through 48 Weeks[1]

	SYMTUZA (n=362)	Control (n=363)
Any AE regardless of causality, n (%)	312 (86)	307 (85)
Any study drug-related AE, n (%)	126 (35)	151 (42)
Any grade 3 or 4 AE regardless of causality, n (%)	19 (5)	22 (6)
Any SAE regardless of causality[a], n (%)	17 (5)	21 (6)
AEs leading to permanent discontinuation[b], n (%)	7[c] (2)	16 (4)
Death[d], n (%)	0	0
Most common AEs regardless of causality (≥5% of patients in either group), n (%)		
Diarrhea[e]	71 (20)	66 (18)
Headache	47 (13)	32 (9)
Nasopharyngitis	40 (11)	31 (9)
Rash	32 (9)	25 (7)
Nausea	28 (8)	45 (12)
Upper respiratory tract infection	20 (6)	21 (6)
Fatigue	19 (5)	18 (5)
Syphilis	17 (5)	19 (5)
Osteopenia	17 (5)	27 (7)
Bronchitis	14 (4)	19 (5)
AEs at least possibly related to study drug (≥5% of patients in either group), n (%)		
Diarrhea[e]	31 (9)	40 (11)
Rash	22 (6)	14 (4)
Nausea	20 (6)	36 (10)
change from baseline in fasting lipids at week 48		
Total cholesterol, median (IQR), mg/dL	+28.6 (+12.8–47.2)[f]	+10.4 (-8.0–29.8)
HDL-C, median (IQR), mg/dL	+4.3 (-1.2–12.0)[f]	+1.5 (-3.9–8.1)
LDL-C, median (IQR), mg/dL	+17.4 (+2.9–32.9)[f]	+5.0 (-10.8–19.0)
Triglycerides, median (IQR), mg/dL	+23.9 (-3.0–58.5)[f]	+14.2 (-12.0–40.7)
Total cholesterol/HDL-C ratio, median (IQR)	+0.20 (-0.28–0.67)[f]	+0.08 (-0.41–0.53)

Abbreviations: AE, adverse event; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SAE, serious adverse event.
[a]Considered study drug-related in 0 (SYMTUZA group) vs 6 patients (1.7% control) (rash and toxic skin eruption in 2 patients each, and bone marrow edema and Stevens-Johnson syndrome in 1 patient each).
[b]SYMTUZA (n=7): rash (n=4), generalized rash, maculopapular rash, diarrhea; control (n=16): rash/erythema (n=7), toxic skin eruption (n=2), neoplasms (n=2), Stevens-Johnson syndrome, diarrhea, bone marrow edema, increased beta-2-microglobulin, and arthralgia.
[c]One fewer patient in the SYMTUZA group had an AE assessed as leading to discontinuation since data are taken from the AE electronic case report form (whether or not the drug was withdrawn), and the patient had interrupted treatment.
[d]One death occurred in the control arm, but in follow-up (not considered related to study drug).
[e]The majority of episodes of diarrhea were mild: grade 1: 16% vs 13% (related: 7% vs 9%) and grade 2: 4% vs 5% (related: 2% vs 2%).
[f]$P<0.0001$ (total cholesterol, HDL-C, LDL-C), $P=0.001$ (triglycerides), $P=0.036$ (total cholesterol/HDL-C ratio) for SYMTUZA group vs control group.

- Safety data through 96 weeks is reported in Table: AEs Through 96 Weeks.[2]
  - The incidences of AEs in the SYMTUZA arm were similar between the overall population and the subgroups of age, gender, race, baseline VL, baseline $CD4^+$ cell count, and WHO clinical stage.[3]
  - In the SYMTUZA arm, there were statistically significant increases from baseline to week 96 in fasting total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and total cholesterol/HDL-C ratio ($P>0.001$ for within treatment arm changes).
    - Similar increases in median lipid parameter values were observed in the subgroups of age, gender, and race.[3]
  - Grade 3 or 4 fasting LDL-C (≥190 mg/dL) occurred in 9% (30/346) of patients in the SYMTUZA arm and 4% (11/295) of patients in the control arm after switch to SYMTUZA.

- Lipid-lowering drugs were started by 14 (4%) patients by week 96 in the SYMTUZA arm and 3 (1%) of patients in the control arm after switch to SYMTUZA.

AEs Through 96 Weeks[2]

Incidence	SYMTUZA Arm		Control	
	Baseline-Week 48 (n=362)	Baseline-Week 96 (n=362)	DRV/COBI +TDF/FTC (Baseline-Switch) N=363	SYMTUZA (Switch-Week 96) N=295
Patient-years exposure[a]	323	626	512	109
≥1 AE, any grade, n (%)	312 (86)	334 (92)	326 (90)	125 (42)
Study drug-related AEs, n (%)	128 (35)	142 (39)	158 (44)	14 (5)
Study drug-related AEs (≥5%), n (%)				
Diarrhea	33 (9)	34 (9)[b]	42(12)	1 (<1)
Rash	22 (6)	22 (6)	14 (4)	1 (<1)
Nausea	20 (6)	20 (6)	36 (10)	3 (1)
Study drug-related grade 3-4 AEs, n (%)	6 (2)	11 (3)	6 (2)	3 (1)
≥1 serious AE, n (%)	17 (5)	39 (11)	36 (10)	8 (3)
Study drug-related serious AEs, n (%)	0	1 (<1)	6 (2)	0
≥1 AE leading to discontinuation, n (%)	8 (2)	10 (3)	17 (5)	1 (<1)

Abbreviation: AE, adverse event.
[a]Patient-years of exposure = sum of treatment duration (weeks) x 7 /365.25.
[b]All cases were mild: 27 grade 1 and 7 grade 2.

Renal Safety

- There were no study drug-related discontinuations due to renal AEs in either treatment arm through 96 weeks.[2]
- At week 96, renal AEs regardless of causality occurred in 5% (17/362) of patients (SYMTUZA arm), with dysuria (n=4), hematuria (n=3), renal colic and urethral discharge (each n=2) occurring in ≥2 patients.
- No renal AEs occurred in control arm after switch to SYMTUZA.
- There were no cases of Fanconi syndrome or subclinical proximal renal tubulopathy reported in either arm through week 96.
- SCr increased from baseline to week 48 in the SYMTUZA group (+4.8 µmol/L), consistent with cobicistat inhibition of creatinine tubular secretion, but less so than in the control group (+8.2 µmol/L) (P<0.0001).
- No clinically relevant changes in eGFR occurred through week 96 in the SYMTUZA arm or control arm in the overall population; results were consistent across subgroups.[3]
- In the SYMTUZA arm (overall population):
  - The median change (decrease) in $eGFR_{cr}$ at week 96 was -5.6 mL/min/1.73 m² (P<0.001 within treatment arm change from baseline).
  - The median change (increase) in eGFR based on cystatin C at week 84 was +3.2 mL/min/1.73 m².
- At week 48, all quantitative measures demonstrated less proteinuria for SYMTUZA vs control, as determined by mean changes from baseline in urine protein/creatinine ratio (-22.42 vs -10.34 mg/g; P=0.033), urine albumin/creatinine ratio (-2.45 mg/g vs -0.58 mg/g; P=0.003), urinary retinol binding protein/creatinine ratio (16.84 µg/g vs 401.12 µg/g; P<0.0001), and beta-2-microglobulin/creatinine ratio (-100.58 µg/g vs 837.63 µg/g; P<0.0001).[1]
- Improvements in proteinuria were maintained through week 96 in the SYMTUZA arm vs control arm, as determined by median changes from baseline in urine protein/creatinine ratio (-15.5 vs -10.5 mg/g), urine albumin/creatinine ratio (-0.7 vs -0.2), urinary retinol

binding protein/creatinine ratio (13.7 vs 35.1 ug/g), and beta-2-microglobulin/creatinine ratio (-27 vs 18.4 ug/g); all *P*<0.001 for within treatment arm changes at week 96 from baseline.[2] Results were consistent across subgroups.[3]

Bone Safety

- Over 48 weeks, BMD was stable at the hip, lumbar spine, and femoral neck for SYMTUZA (mean percentage change +0.21%, -0.68%, and -0.26%, respectively) vs decreases for controls (-2.73%, -2.38%, and -2.97%, respectively; *P*<0.0001 hip and femoral neck and *P*=0.004 spine, between-treatment comparisons).[1]
    - The percentage of patients with ≥3% increase in BMD was 12.5% vs 2.4% for hip, 12.5% vs 4.7% for spine, and 14.6% vs 7.1% for femoral neck in the SYMTUZA and control groups, respectively, through week 48.
    - The percentage of patients with ≥3% decrease in BMD was 12.5% vs 44.7% for hip, 27.1% vs 41.2% for spine, and 21.9% vs 52.9% for femoral neck in the SYMTUZA and control groups, respectively, through week 48.
    - Fractures occurred in 1.1% (4/362) of patients in the SYMTUZA group and in 0.6% (2/363) of patients in the control group over 48 weeks; all were traumatic and none were suspected to be osteoporotic.
    - New anti-osteoporotic treatment was started by 9/362 (2.5%) vs 16/363 (4.4%) patients, respectively, during the treatment phase (through week 48).
    - Improvements in renal function and changes in BMD were similar between age, gender, and race subgroups over 48 weeks.[5]
- In the SYMTUZA arm, there was no change in hip BMD, with a small decrease in lumbar spine BMD and femoral neck BMD through week 96 (mean percentage change from baseline -0.3% [*P*=0.47], -0.9% [*P*=0.04], and -1.3% [*P*=0.005], respectively).[2]
    - The percentage of patients with ≥3% increase in BMD was 17% for hip, 16% for spine and 11% for femoral neck, respectively.
    - The percentage of patients with ≥3% decrease in BMD was 23% for hip, 34% for spine and 30% for femoral neck, respectively.
- In the control arm following switch to SYMTUZA, small numerical increases in BMD were observed at each site through week 96 (+0.5% for hip, spine and +0.2% for femoral neck).
- In subgroup analyses, small decreases in BMD of the hip, lumbar spine, and femoral neck were observed across the demographic subgroups of age, gender, and race in the SYMTUZA arm through week 96.[3]
- In the SYMTUZA arm, there was no change in alkaline phosphatase and minimal changes in procollagen type N-terminal propeptide and C-type collagen sequence through week 96.

Neurologic/Psychiatric Adverse Effects

- In a subgroup analysis through week 48, patient with neuropsychiatric comorbidities (NPCs) did not experience higher rates of study-drug related AEs compared with those without baseline NPCs.[6]

Gastrointestinal Adverse Effects

- In a subgroup analysis, the incidence of SYMTUZA-related GI AEs of interest was low, tended to present early in the study, and rapidly decreased thereafter.[10]
    - The incidence of SYMTUZA-related diarrhea and nausea was 5% for each during week 1 and decreased to ≤1% after week 2.
    - The prevalence of SYMTUZA-related diarrhea decreased to <5% starting at week 2, and the prevalence of SYMTUZA-related nausea decreased to <3% by week 2 and <1% by week 5.

- One case of SYMTUZA-related abdominal discomfort was reported (week 1), and the incidence of SYMTUZA-related flatulence was <1% through week 96.

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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