SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
Safety Information of SYMTUZA - Effect on Lipids

SUMMARY

- In the AMBER study, there was a statistically significant increase in all lipid parameters from baseline to week 48.[1] In the SYMTUZA arm, lipid-lowering drugs were started by 6 (1.7%) and 14 (4%) of patients by weeks 48 and 96, respectively.[2]
- In the EMERALD study, lipid-lowering drugs were started by 20/763 (3%) patients in the SYMTUZA arm vs. 7/378 (2%) patients in the boosted protease inhibitor (bPI) arm by week 48,[3] and by 59/763 (8%) patients in the SYMTUZA arm vs. 19/352 (5%) patients in the control arm by week 96.[4]
- In the GS-US-299-0102 study, there were greater increases in fasting lipid parameters in the SYMTUZA arm compared with the darunavir (DRV)+ cobicistat (COBI)+ emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) arm at week 48.[5]
- In the DETOX study, there was a significant increase in triglycerides, low-density lipoprotein (LDL) cholesterol, and total cholesterol from baseline to week 8, whereas high-density lipoprotein (HDL) cholesterol remained stable.[6]

CLINICAL DATA

AMBER

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

Study Design/Methods

- Patients were stratified by screening viral load (VL;< / ≥100,000) and by screening cluster of differentiation (CD) 4+ cell counts (< / ≥200 cells/mm^3) and then randomized to a single-tablet regimen (STR) of SYMTUZA (DRV 800 mg, COBI 150 mg, FTC 200 mg, and tenofovir alafenamide [TAF] 10 mg) with matching DRV/COBI + FTC/TDF placebo or the active-control regimen of DRV/COBI + FTC/TDF with a matching SYMTUZA placebo.
- After database lock and unblinding for the week 48 analysis, patients randomized to SYMTUZA continued on open-label SYMTUZA and patients randomized to the DRV/COBI + FTC/TDF control arm were switched to SYMTUZA in the extension phase until week 96.

Results-Week 48

- There was a statistically significant increase in all lipid parameters from baseline to week 48, see Table: Median (IQR) Change from Baseline in Fasting Lipids at Week 48.
- There were 6 (1.7%) patients in the SYMTUZA arm who started lipid lowering therapy compared to 2 (0.6%) patients in the control arm.

Median (IQR) Change From Baseline in Fasting Lipids at Week 48[1]

Assessment	SYMTUZA (n=362)	Control (n=363)	*P* Value
Total cholesterol, mg/dL	+28.6 (+12.8 to 47.2)	+10.4 (-8.0 to 29.8)	<0.0001
HDL cholesterol, mg/dL	+4.3 (-1.2 to 12.0)	+1.5 (-3.9 to 8.1)	<0.0001
LDL cholesterol, mg/dL	+17.4 (+2.9 to 32.9)	+5.0 (-10.8 to 19.0)	<0.0001
Triglycerides, mg/dL	+23.9 (-3.0 to 58.5)	+14.2 (-12.0 to 40.7)	0.001
Total cholesterol/HDL cholesterol ratio	+0.20 (-0.28 to 0.67)	+0.08 (-0.41 to 0.53)	0.036
Abbreviations: HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.			

Results-Week 96[2]

- In the SYMTUZA arm, there were statistically significant increases from baseline to week 96 in fasting total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and total cholesterol/HDL-cholesterol ratio (P<0.001 for within treatment arm changes).
- Grade 3 or 4 fasting LDL-cholesterol (≥190 mg/dL [4.90 mol/L]) occurred in 9% (30/346) of patients in the SYMTUZA arm from baseline-week 96 and 4% (11/295) of patients in the control arm after switch to SYMTUZA.
- Fasting lipid parameters are shown in Table: Fasting Lipids.
- 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.

Fasting Lipids[2]

Median Value	Baseline		Week 48		Week 96
	SYMTUZA	Control	SYMTUZA	Control	SYMTUZA
Total cholesterol, mg/dL	163	162	196	172	200[a]
LDL cholesterol, mg/dL	96	97	116	101	123[a]
HDL cholesterol, mg/dL	42	42	48	44	47[a]
Triglycerides, mg/dL	97	95	123	112	130[a]
Total cholesterol/HDL cholesterol ratio	3.8	3.8	4.0	3.9	4.2[a]

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]P<0.001 for within treatment arm changes at week 96 from baseline (Wilcoxon signed-rank test).

EMERALD

The EMERALD study is a phase 3, randomized, active-controlled, open-label 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 (N=1141).[3]

Study Design/Methods

- Patients were stratified according to PI (DRV/ritonavir [r] or DRV/COBI once daily [QD], atazanavir [ATV]/r or ATV/COBI QD, or lopinavir [LPV]/r twice daily [BID]) and then randomized 2:1 to switch to SYMTUZA or to continue their bPI regimen.
- After week 48, patients randomized to SYMTUZA continued on SYMTUZA and patients randomized to the bPI arm were switched to SYMTUZA in the extension phase until week 96.[4]

Results-Week 48[3]

- Median changes from baseline to week 48 (SYMTUZA vs. bPI):
  - Fasting total cholesterol: 19.7 mg/dL vs. 1.3 mg/dL (P<0.0001)
  - LDL-cholesterol: 15.7 mg/dL vs. 1.9 mg/dL (P<0.0001)
  - Ratio of total cholesterol to HDL-cholesterol: 0.2 vs. 0.1 (P=0.010)
- During treatment, lipid-lowering drugs were started by 20/763 (3%) patients in the SYMTUZA arm vs. 7/378 (2%) patients in the bPI arm (P=0.54).
- For treatment emergent AEs, see Table: Treatment-Emergent Grade 3-4 Laboratory AEs (≥3% in Either Arm)

Treatment-Emergent Grade 3-4 Laboratory AEs (≥3% in Either Arm)[3]

Parameter, n (%)	SYMTUZA (N=763)	bPI (N=378)
Fasting LDL (≥4.90 mol/L; 190 mg/dL)	48 (7)	6 (2)
Fasting total cholesterol (≥7.77 mol/L; ≥300 mg/dL)	28 (4)	5 (1)
Abbreviations: AE, adverse event; bPI, boosted protease inhibitor; LDL, low-density lipoprotein.		

Results-Week 96[4]

- Treatment-emergent grade 3 or 4 laboratory abnormalities are shown in Table. Most Common Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities (>5% Either Arm).
- Median change in fasting lipid parameters are shown in Table. Median (IQR) Change in Fasting Lipids.
- In the SYMTUZA arm, fasting lipid parameters remained stable after week 48.
- By week 96, lipid-lowering drugs were started by 59/763 (8%) patients in the SYMTUZA arm vs. 19/352 (5%) patients in the control arm.

Most Common Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities (>5% Either Arm)[4]

	SYMTUZA Arm			Late Switch Arm	
	SYMTUZA (BL-Week 48) (N=763)	SYMTUZA (Weeks 48-96) (N=728)	SYMTUZA (BL-Week 96) (N=763)	bPI (BL-Week 52) (N=378)	SYMTUZA[a] (Weeks 52-96) (N=352)
Fasting LDL (≥4.90 mol/L; ≥190 mg/dL)	47/737 (6)	38/688 (6)	67/741 (9)	6/364 (2)	9/328 (3)
Fasting total cholesterol (≥7.77 mol/L; ≥300 mg/dL)	27/737 (4)	16/692 (2)	36/741 (5)	5/364 (1)	6/330 (2)
Abbreviations: BL, baseline; bPI, boosted protease inhibitor; LDL, low-density lipoprotein. [a] Comprising 44 weeks of SYMTUZA exposure (ie, from the switch to SYMTUZA at week 52).					

Median (IQR) Change in Fasting Lipids[4]

	SYMTUZA Arm				Late Switch Arm		
	SYMTUZA (BL-Week 48) (N=763)	SYMTUZA (Weeks 48-96) (N=728)	SYMTUZA (BL-Week 96) (N=763)	*P* Value[a,b]	bPI (BL-Week 52) (N=378)	SYMTUZA[c] (Weeks 52- 96) (N=352)	*P* Value[a,b]
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, 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, 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 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: BL, baseline; bPI, boosted protease inhibitor; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; ND, not determined.
[a]Within treatment arm comparisons for change at week 96 from reference assessed by Wilcoxon signed-rank test.
[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).

GS-US-299-0102

In the GS-US-299-0102 study, the efficacy and safety of the SYMTUZA STR was compared to that of DRV + COBI (administered as single agents) + FTC/TDF in HIV-1 infected, treatment-naïve patients (N=153).[5]

Study Design/Methods

- Patients were stratified by baseline VL (≤100,000 and >100,000) and race (black and non-black) and randomized 2:1 to receive an STR containing SYMTUZA (DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg) [TAF arm]), or a regimen consisting of DRV 400 mg x 2 + COBI 150 mg + FTC/TDF 200/300 mg tablets (TDF arm).

Results

- There were greater increases in fasting lipid parameters in the TAF arm compared with the TDF arm at week 48, see Table: Median Change from Baseline in Fasting Lipids at Week 48.
- The majority of reported lipid-related adverse events and laboratory abnormalities were nonserious and mild in severity.
- There were no differences in the number of patients who were initiated on lipid-lowering medications during the study (TAF, 7 [6.8%] vs. TDF, 4 [8%], *P*=0.75).

Median Change From Baseline in Fasting Lipids at Week 48[5]

Assessment	SYMTUZA (N=103)	DRV + COBI + FTC/TDF (N=50)	*P* Value
Total cholesterol, mg/dL	40	5	<0.001
LDL, mg/dL	26	4	<0.001
HDL, mg/dL	7	3	0.009
Total cholesterol:HDL ratio	0.0	-0.2	0.15
Triglycerides	29	-5	0.007

Abbreviations: COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TDF, tenofovir disoproxil fumarate.

DETOX

DETOX was a randomized, open-label study that was conducted in 2 phases to evaluate whether switching from dolutegravir (DTG)/lamivudine (3TC)/abacavir (ABC) to SYMTUZA could help in improving the quality of sleep, mood, and neuropsychiatric status in virologically-suppressed, human immunodeficiency virus (HIV)-infected adults.[6]

Study Design/Methods

- Phase 1: Patients were randomized to switch at baseline from DTG/3TC/ABC to SYMTUZA (immediate switch arm; n=37) or to continue 4 weeks with DTG/3TC/ABC and then switch to SYMTUZA (deferred switch arm; n=35).

- Phase 2: Patients from both the arms completed 8 weeks of follow-up after switching to SYMTUZA.
- Patients with HIV who had no major neuropsychiatric comorbidities (major depression with psychotic symptoms or suicidal ideation, drug abuse/dependence, dementia, or psychosis), were receiving DTG/3TC/ABC for at least 4 weeks, had poor quality of sleep (PSQI score >5), and did not complain of insomnia were included.
- Changes in lipid parameters were evaluated as part of the safety analysis.

Results

- From baseline to week 8, a significant increase in total cholesterol, LDL cholesterol, and triglycerides was observed, whereas HDL cholesterol remained stable (see Table: Mean Lipids Levels at Baseline, Week 4, and Week 8).

Mean Lipids Levels at Baseline, Week 4, and Week 8[6]

Mean±SE, mg/dL	Baseline Before Switching to SYMTUZA	Week 4 After Switching to SYMTUZA	Week 8 After Switching to SYMTUZA	*P* Value[a]
Total cholesterol	181.2±3.5	200.7±4.2	203.8±4	<0.001
LDL cholesterol	109.4±2.7	124.2±3.6	125.4±3.3	<0.001
Triglycerides	132.9±10.5	160.9±10.5	157.8±9.6	0.021
HDL cholesterol	47.1±1.5	47.4±1.5	47.4±1.4	1

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error.
[a]Changes from baseline to week 8.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 22 August 2023.

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