PREZCOBIX® (darunavir/cobicistat)
PREZCOBIX - Safety Information - Effect on Lipids

SUMMARY

- In the GS-US-216-0130 study, no clinically relevant changes from baseline through week 48 in median fasting total cholesterol (TC), median fasting low-density lipoprotein cholesterol (LDL), median fasting high-density lipoprotein cholesterol (HDL), median fasting triglycerides (TG), or median fasting TC to HDL ratio were observed in patients who received darunavir (DRV) and cobicistat (COBI).[1-3]
- A study conducted in virologically suppressed patients who were receiving a stable regimen containing darunavir (DRV)/ritonavir (r) and were then switched from ritonavir to COBI found that COBI had a beneficial effect on TG levels in all patients. Statistically significant changes in all lipid parameters were observed in patients with baseline hypercholesterolemia.[4]
- In the AMBER study, which compared PREZCOBIX + emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) with the single-tablet regimen (STR) DRV/COBI/FTC/tenofovir alafenamide (TAF), there was a statistically significant increase in all lipid parameters from baseline to week 48. Lipid-lowering drugs were started by 6 (1.7%) patients in the STR arm and 2 (0.6%) patients in the PREZCOBIX arm by week 48, and 14 (4%) patients in the STR arm vs. 3 (1%) patients in the PREZCOBIX arm by week 96.[5, 6]
- In the GS-US-299-0102 study, there were greater increases in fasting lipid parameters in the STR (DRV/COBI/FTC/TAF) group compared with the DRV + COBI + FTC/TDF group at week 48.[7]
- In the EMERALD study, lipid-lowering drugs were started by 20/763 (3%) patients in the STR (DRV/COBI/FTC/TAF) arm vs. 7/378 (2%) patients in the boosted protease inhibitor (bPI) + FTC/TDF arm by week 48, and by 59/763 (8%) patients in the STR arm vs. 19/352 (5%) patients in the control arm by week 96.[8, 9]

CLINICAL STUDIES

GS-US-216-0130 Study

GS-US-216-0130 is a phase 3b, open-label, single arm, 48 week, multicenter US study evaluating the safety, tolerability, efficacy, and pharmacokinetics of DRV 800 mg + COBI 150 mg once daily (QD; administered as single agents) in combination with 2 fully active nucleoside reverse transcriptase inhibitors (NRTIs) in treatment-naïve and treatment-experienced (no DRV RAMs) HIV-1-infected patients (N=313; n=295 treatment-naïve).[1]

Lipid Evaluations

Week 24-Lipids

- Through week 24, 4 patients (1.3%) each experienced hypercholesterolemia and hypertriglyceridemia, and 3 patients (1.0%) experienced increased blood TG.[2]
  - All but 1 of these patients (hypertriglyceridemia) were treatment-naïve.
  - A total of 3 patients experienced grade 3 hypercholesterolemia, and a total of 4 patients experienced a grade 3 increase in TG. All of these patients were treatment-naïve.
  - No subject experienced a serious adverse event (AE) associated with a clinical laboratory abnormality, and no subject discontinued with study drugs or the study due to an AE associated with a clinical laboratory abnormality.
- There were no clinically relevant changes from baseline through week 24 observed in either the treatment-naïve or treatment-experienced cohorts for median fasting TC, median fasting LDL, median fasting HDL, median fasting TG, or median fasting TC to HDL ratio.[2]

- There were no apparent relationships observed between DRV area under the concentration-time curve during a 24-hour interval (AUC_{24h}) and worst toxicity grade in TC, LDL, HDL, or TG through week 24.[2]
    - Higher DRV AUC_{24h} and trough plasma concentrations (C_{0h}) were observed in patients with grade 3 cholesterol changes. This analysis was limited by a small sample size (n=4).

Week 48-Lipids

- There were no clinically relevant changes from baseline in median lipid parameters through week 48.[1]

Lipid Parameters at Baseline, Week 24, and Week 48[3]

Parameter, mg/dL	Treatment-naïve patients			Treatment-experienced patients			All patients		
	N	Median	Range	N	Median	Range	N	Median	Range
TG									
Baseline	290	95	35-1252	18	124	56-1378	308	97	35-1378
Week 24	259	117	28-790	16	151	55-918	275	120	28-918
Week 48	244	115	41-780	15	133	59-643	259	116	41-780
TC									
Baseline	290	159	70-290	18	160	76-454	308	159	70-454
Week 24	260	175	89-317	16	190	46-302	276	175	46-317
Week 48	244	176	87-291	15	180	61-283	259	176	61-291
LDL									
Baseline	291	103	31-224	18	99	46-177	309	102	31-224
Week 24	260	111	39-235	16	109	13-206	276	111	13-235
Week 48	245	112	41-233	15	116	29-196	260	112	29-233
HDL									
Baseline	290	43	19-122	18	42	15-60	308	43	15-122
Week 24	261	45	10-97	16	46	14-68	277	45	10-97
Week 48	243	44	20-93	15	43	17-54	258	44	17-93

Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Echeverria Study

Echeverria et al (2017)[4] evaluated changes in lipid parameters and the percentage of subjects with dyslipidemia in virologically suppressed HIV-1 infected patients who were receiving a stable regimen containing DRV/r (monotherapy, dual therapy, or triple therapy for ≥6 months) and were then switched from ritonavir to COBI (N=299).

Study Design/Methods

- Retrospective observational study.
- Lipid parameters at baseline before the switch and 24 weeks after the switch were compared.
- Patients were stratified according to the presence of hypercholesterolemia (taking lipid-lowering drugs or baseline TC >200 mg/dL and/or LDL >130 mg/dL) or hypertriglyceridemia (baseline TG levels >200 mg/dL).

Results

Baseline Characteristics

- Epidemiological, clinical, and human immunodeficiency virus (HIV)-related characteristics are summarized in Table: Baseline Characteristics.
- Fifty-two percent of patients had dyslipidemia (hypercholesterolemia and/or hypertriglyceridemia) at baseline; of these, 52% were on monotherapy, 61% were on dual therapy, and 70% were on triple therapy.

Baseline Characteristics[4]

	N=299
Age (years), median (IQR)	49 (42, 54)
Gender (male) (%)	85
HCV coinfection (%)	6
HBV coinfection (%)	2
Cumulative exposure to ARV therapy (years), median (IQR)	12 (6, 20)
Cumulative exposure to protease inhibitors (years), median (IQR)	7.5 (4, 14)
Current CD4+ count (cells/mm^3), median (IQR)	646 (448, 847)
CD4+ count <200 cells/µL (%)	5.4
VL ≤50 copies/mL (%)	100
ARV treatment (%)	
DRV/r monotherapy	49.5
DRV/r dual therapy	9
DRV/r triple therapy	41.5
Receiving TDF	26
Abbreviations: ARV, antiretroviral; DRV, darunavir; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; r, ritonavir; TDF, tenofovir disoproxil fumarate; VL, viral load.	

Lipid Evaluations

- Changes in lipid parameters are detailed in Table: Changes in Lipid Parameters at Week 24.
- In the study population as a whole or in the subset with baseline hypertriglyceridemia, only TG decreased significantly from baseline; significant changes in other lipids were not observed.
- In the subset with baseline hypercholesterolemia, changes from baseline to week 24 were significant for all lipid parameters.

Changes in Lipid Parameters at Week 24[4]

Lipid Parameter	**Baseline (N=299)**	**Week 24 after change**	***P*-value**
Use of lipid-lowering agents (%)	12	12	-
TC (mg/dL), median (IQR)	190 (162, 216)	184 (154, 211)	0.085
LDL (mg/dL), median (IQR)	111 (92, 136)	109 (84, 132)	0.530
HDL (mg/dL), (median [IQR])	44 (38, 54)	45 (38, 54)	0.440
TG (mg/dL), median (IQR)	167 (93, 187)	124 (87, 175)	0.018
Subjects with hypercholesterolemia at baseline (TC >200 mg/dL and/or LDL >130 mg/dL) (n=124)			
TC (mg/dL), median (IQR)	231 (209, 243)	212 (189, 239)	0.001
LDL (mg/dL), median (IQR)	144 (131, 161)	131 (113, 152)	0.047
HDL (mg/dL), median (IQR)	45 (40, 54)	52 (44, 59)	0.002
TG (mg/dL), median (IQR)	157 (109, 209)	131 (101, 202)	0.025
Subjects with TG >200 mg/dL at baseline (n=64)			
TC (mg/dL), median (IQR)	207 (182, 232)	191 (158, 215)	0.067
LDL (mg/dL), (median (IQR)	109 (84, 121)	105 (83, 127)	0.299
HDL (mg/dL), median (IQR)	40 (36, 45)	40 (36, 48)	0.381
TG (mg/dL), median (IQR)	352 (223, 389)	229 (131, 279)	<0.001
Abbreviations: HDL, high-density lipoprotein cholesterol; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.			

DATA FROM STUDIES WITH DRV/COBI/FTC/TAF STR

AMBER

The AMBER study is a phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of the STR DRV/COBI/FTC/TAF vs. the fixed-dose combination PREZCOBIX co-administered with FTC/TDF in antiretroviral (ARV) treatment-naïve HIV-1-infected adults (N=725).[5]

Study Design/Methods

- Patients were stratified by screening viral load (VL;</≥100,000) and by screening CD4+ cell counts (</≥200 cells/mm^3) and then randomized to receive the STR (DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg) with matching PREZCOBIX + FTC/TDF placebo or the active-control regimen of PREZCOBIX + FTC/TDF with a matching STR placebo.
- After database lock and unblinding for the week 48 analysis, patients randomized to the STR continued on open-label DRV/COBI/FTC/TAF and patients randomized to the PREZCOBIX + FTC/TDF control arm were switched to DRV/COBI/FTC/TAF in the extension phase until week 96.

Results – Week 48[5]

- There was a statistically significant increase in all lipid parameters from baseline to week 48 (Table. Median (Interquartile Range [IQR]) Change from Baseline in Fasting Lipids at Week 48).
- There were 6 (1.7%) patients in the STR arm who started lipid lowering therapy compared to 2 (0.6%) patients in the PREZCOBIX + FTC/TDF arm.

Median (IQR) Change from Baseline in Fasting Lipids at Week 48[5]

Assessment	DRV/COBI/FTC/TAF (N=362)	PREZCOBIX + FTC/TDF (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: COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Results – Week 96[6]

- In the initial STR 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 STR arm from baseline-week 96 and 4% (11/295) of patients in the PREZCOBIX + FTC/TDF arm after switch to the STR.
- Fasting lipid parameters are shown in Table: Fasting Lipids.
- Lipid-lowering drugs were started by 14 (4%) patients by week 96 in the STR arm and 3 (1%) of patients in the PREZCOBIX + FTC/TDF arm after switch to the STR.

Fasting Lipids[6]

Median Value	Baseline		Week 48		Week 96
	DRV/COBI/ FTC/TAF	PREZCOBIX + FTC/TDF	DRV/COBI/ FTC/TAF	PREZCOBIX + FTC/TDF	DRV/COBI/ FTC/TAF
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: COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
[a]*P*<0.001 for within treatment arm changes at week 96 from baseline (Wilcoxon signed-rank test).

GS-US-299-0102

In the GS-US-299-0102 study, the efficacy and safety of the DRV/COBI/FTC/TAF STR was compared to that of DRV + COBI (administered as single agents) + FTC/TDF in HIV-1 infected, treatment-naïve patients (N=153).[7]

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 the STR (DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg; TAF group) or a regimen consisting of DRV 400 mg x 2 + COBI 150 mg + FTC/TDF 200/300 mg tablets (TDF group).

Results

- There were greater increases in fasting lipid parameters in the TAF group compared with the TDF group at week 48 (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[7]

Assessment	DRV/COBI/FTC/TAF (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; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

EMERALD

The EMERALD study is a phase 3, randomized, active-controlled, open-label study to evaluate the efficacy, safety, and tolerability of switching to the DRV/COBI/FTC/TAF STR vs. continuing the current regimen consisting of a bPI combined with FTC/TDF in virologically-suppressed, HIV-1-infected adults (N=1141).[8]

Study Design/Methods

- Patients were stratified according to PI (DRV/r or PREZCOBIX QD, atazanavir [ATV]/r or ATV/COBI QD, or lopinavir [LPV]/r BID) and then randomized 2:1 to switch to the STR (DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg) or to continue their bPI regimen.
- After week 48, patients randomized to the STR continued on DRV/COBI/FTC/TAF and patients randomized to the bPI arm were switched to DRV/COBI/FTC/TAF in the extension phase until week 96.[9]

Results- Week 48[8]

- Median changes from baseline to week 48 (STR vs. bPI + FTC/TDF):
  - 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 STR arm vs. 7/378 (2%) patients in the bPI arm (*P*=0.54).

Treatment-Emergent Grade 3-4 Laboratory AEs (≥3% in Either Arm)[8]

Parameter, n (%)	DRV/COBI/FTC/TAF (N=763)	bPI + FTC/TDF (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: AEs, adverse events; bPI, boosted protease inhibitor; COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; LDL, low-density lipoprotein; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Results – Week 96[9]

- 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 initial STR arm, fasting lipid parameters remained stable after week 48.
- By week 96, lipid-lowering drugs were started by 59/763 (8%) patients in the initial STR arm vs. 19/352 (5%) patients in the late switch arm.

Most Common Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities (>5% Either Arm)[9]

	Initial DRV/COBI/FTC/TAF Arm			Late Switch Arm	
	STR (BL-week 48) (N=763)	STR (week 48-week 96) (N=728)	STR (BL-week 96) (N=763)	bPI + FTC/TDF (BL-week 52) (N=378)	STR[a] (week 52-week 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; COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; LDL, low-density lipoprotein; ND, not determined; STR, single-tablet regimen of DRV/COBI/FTC/TAF; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
[a] Comprising 44 weeks of DRV/COBI/FTC/TAF exposure (ie, from the switch to the STR at week 52).

Median (IQR) Change in Fasting Lipids[9]

	Initial DRV/COBI/FTC/TAF Arm			Late Switch Arm		
	STR (BL-week 48) (N=763)	STR (BL-week 96) (N=763)	*P*-value[a,b]	bPI + FTC/TDF (BL-week 52) (N=378)	STR[c] (week 52-96) (N=352)	*P*-value[a,b]
TC, mg/dL	+19.9 (1.2; 39.4)	+22.0 (0.4; 44.0)	<0.001	+1.3 (-12.0; 20.0)	+22.0 (3.0; 42.7)	<0.001
HDL, mg/dL	+2.7 (-3.0; 8.0)	+3.0 (-2.0; 8.5)	<0.001	0.0 (-4.6; 4.0)	+3.3 (-2.0; 8.0)	<0.001
LDL, mg/dL	+15.9 (0.0; 32.0)	+17.0 (-3.0; 35.2)	<0.001	+1.9 (-12.0; 17.0)	+15.0 (0.0; 32.9)	<0.001
TG, mg/dL	+5.7 (-21.0; 39.0)	+7.0 (-25.0; 43.0)	<0.001	+4.9 (-23.0; 39.0)	+8.0 (-25.8; 47.0)	0.004
TC:HDL ratio	+0.20 (-0.20; 0.60)	+0.20 (-0.40; 0.70)	<0.001	+0.10 (-0.30; 0.40)	+0.20 (-0.30; 0.70)	<0.001

Abbreviations: BL, baseline; bPI, boosted protease inhibitor; COBI, cobicistat; DRV, darunavir; FTC, emtricitabine; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; STR, single-tablet regimen of DRV/COBI/FTC/TAF; TAF, tenofovir alafenamide; TC, total cholesterol; TDF, tenofovir disoproxil fumarate; TG, triglycerides.
[a]Within treatment arm comparisons for change at week 96 from reference assessed by Wilcoxon signed-rank test.
[b]Reference for the initial STR arm is study baseline and for the late switchers is the last value before the switch.
[c]Comprising 44 weeks of DRV/COBI/FTC/TAF exposure (ie, from the switch to the STR at week 52).

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 17 April 2023. Company-sponsored studies and studies specifically evaluating DRV/COBI and effect on lipid parameters were included.

REFERENCES

1. Tashima K, Crofoot G, Tomaka FL, et al. Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a phase IIIb, open-label single-arm trial. *AIDS Res Ther*. 2014;11(39):1-12.

2. Data on File. Gilead Sciences, Inc. GS-US-216-0130 Week 24 Clinical Research Report. November 2012.

3. Data on File. Gilead Sciences, Inc. GS-US-216-0130-W48-SAF-LAB-Additional. April 2013.

4. Echeverria P, Bonjoch A, Puig J, et al. Significant improvement in triglyceride levels after switching from ritonavir to cobicistat in suppressed HIV-1-infected subjects with dyslipidemia. *HIV Med*. 2017;18(10):782-786.

5. Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. *AIDS*. 2018;32(11):1431-1442.

6. Orkin C, Eron J, Rockstroh J, et al. Week 96 results of a phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. *AIDS*. 2020;34(5):707-718.

7. Mills A, Crofoot G, McDonald C, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in the first protease inhibitor-based single tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. *J Acquir Immune Defic Syndr*. 2015;69(4):439-445.

8. Orkin C, Molina JM, Negredo E, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. *Lancet HIV*. 2018;5(1):e23-e34.

9. Eron JJ, Orkin C, Cunningham D, et al. 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. *Antiviral Res*. 2019;170:104543.