PREZCOBIX® (darunavir/cobicistat)
PREZCOBIX - Safety Information - Renal Effects

SUMMARY

- The proposed mechanism of the effect of cobicistat (COBI) on estimated glomerular filtration rate (eGFR) is inhibition of the multidrug and toxin extrusion (MATE) efflux protein MATE1. MATE1 is a cationic renal transporter that mediates creatinine secretion.[1]
- COBI affects eGFR but does not affect actual glomerular filtration rate (aGFR).[1]
- GS-US-216-0130 was a phase 3b study which evaluated the safety, tolerability, efficacy, and pharmacokinetics (PK) of darunavir (DRV) 800 mg and COBI 150 mg once daily (QD) administered as single agents in treatment-naïve and treatment-experienced (no DRV resistance-associated mutations [RAMs]) HIV-1-infected patients.[2]
  - Renal laboratory assessments performed through week 48 showed small changes consistent with the inhibitory effects of COBI on renal tubular creatinine secretion rather than a true reduction in glomerular filtration rate (GFR).
  - Through week 48, 1 patient discontinued treatment due to renal tubular disorder which was mild in severity, not serious, and resolved following change in therapy to DRV/ritonavir (r) plus lamivudine (3TC) and abacavir (ABC).
- In GS-US-236-118, the renal safety of COBI was assessed in HIV-1 infected patients with mild to moderate renal impairment (eGFR 50–89 mL/min) who were switched from ritonavir to COBI while continuing a protease inhibitor (PI; atazanavir [ATV] or DRV) and nucleoside reverse transcriptase inhibitor (NRTI) backbone through week 96 (N=73).[3-6]
  - **The results were not reported by the individual PI (ATV or DRV) received.**
  - Through week 96, no cases of proximal renal tubulopathy were reported.[6]
- In a study where virologically suppressed patients were switched from DRV/r to PREZCOBIX, the increase in serum creatinine in patients with moderate renal dysfunction was similar to that observed in patients with eGFR >60 mL/min/1.73 m^2.[7]
- An open-label study evaluating efficacy of switching virologically suppressed patients to boosted DRV + dolutegravir found the decrease in eGFR was similar or lower in patients receiving PREZCOBIX vs DRV/r.[8]
- In a retrospective study conducted in Spain (N=725), higher decreases from baseline in creatinine estimated glomerular filtration rate (Cr-eGFR) were observed with the combination of PREZCOBIX plus rilpivirine and/or dolutegravir than with PREZCOBIX alone at weeks 12, 24, and 48.[9]
- 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), the mean increase in estimated glomerular filtration rate based on serum cystatin C ($eGFR_{cyst}$; Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) at week 48 was greater for the STR (5.3 mL/min/1.73 m^2) than PREZCOBIX + FTC/TDF (2.9 mL/min/1.73 m^2) (P=0.001).[10]
- In the EMERALD study, increases in serum creatinine were larger for patients receiving the STR DRV/COBI/FTC/TAF vs. those in the boosted protease inhibitor (bPI) + FTC/TDF arm (1.3 vs. 0.6 μmol/L; not significant).[11]
- In the GS-US-299-0102 study, the mean change in serum creatinine from baseline at week 48 was 0.06 mg/dL (95% confidence interval [CI], 0.04-0.08) for the TAF group and 0.09 mg/dL (95% CI, 0.05-0.14) for the TDF group (P=0.053).[12]
- In a case report of a patient treated with DRV/COBI/FTC/TAF who developed proximal tubulopathy when treated with gentamicin, serum and urine biochemistry were within normal ranges 11 days after discontinuation of gentamicin without interrupting antiretroviral treatment.

BACKGROUND

The proposed mechanism of COBI's effect on eGFR is inhibition of the MATE efflux protein MATE1. MATE1 is a cationic renal transporter that mediates creatinine secretion.[1]

Administration of COBI 150 mg QD to healthy patients with normal renal function (n=36) and patients with mild or moderate renal impairment (eGFR 50-79 mL/min; n=18) resulted in small increases in serum creatinine. There were corresponding mean decreases in eGFR of approximately 10 mL/min observed on day 7 relative to day 0. eGFR decreases were reversible upon discontinuation of COBI and mean eGFR values returned to baseline on day 14. There were no significant changes in aGFR, as measured by iohexol clearance, on days 7 or 14 relative to day 0.[1]

CLINICAL STUDIES

GS-US-216-0130

Tashima et al (2014)[2] conducted GS-US-216-0130, a phase 3b, open-label, single arm, 48-week, multicenter, US study.

Study Design/Methods

- The GS-US-216-0130 (N=313; n=295 treatment-naïve) study evaluated the safety, tolerability, efficacy, and PK of DRV 800 mg + COBI 150 mg QD (administered as single agents) in combination with 2 fully active NRTIs in treatment-naïve and treatment-experienced (no DRV RAMs) HIV-1-infected patients.[2]

Results

- Patients in the study were required to have an eGFR calculated using the Cockcroft-Gault method ($eGFR_{CG}$) ≥80 mL/min.[2]
- At baseline, the median (range) $eGFR_{CG}$ was 114 (67-321) mL/min in the overall population and 115 (67-321) mL/min among treatment-naïve patients.[2]
- Renal laboratory assessments performed through week 48 showed small changes consistent with the inhibitory effects of COBI on renal tubular creatinine secretion rather than a true reduction in GFR.[2]
    - There was an increase in serum creatinine level from baseline occurring as early as week 2 (median change 0.10 mg/dL), which remained stable throughout the week 48 treatment period (median change 0.09 mg/dL overall and 0.08 mg/dL in treatment-naïve patients).
- Through week 48, 7 patients had confirmed creatinine increases of at least 0.4 mg/dL (range 0.41-0.69 mg/dL) from baseline at 2 or more consecutive visits.[13]
    - None of the 7 patients had ≥grade 1 serum phosphate levels or urine glucose levels, or ≥grade 2 urine protein levels, or experienced treatment-emergent AEs of hypophosphatemia, proteinuria, or glycosuria.
    - In 4 of these patients, the observed change from baseline to last recorded creatinine value was less than 0.4 mg/dL, meaning that the increased creatinine levels observed during the study did not remain elevated, but began to return to the baseline value at or prior to the data cut-off.
    - Three patients had a creatinine increase ≥0.4 mg/dL at the last available time point; 2 of the 3 had no signs of subclinical kidney disease or renal AEs.
    - One patient discontinued treatment due to renal tubular disorder which was mild in severity, not serious, and resolved following a change in therapy to DRV/r plus 3TC and ABC.[2]
- No patient experienced an increase in serum creatinine levels that was considered a grade 3 or 4 abnormality through week 48.[14]

GS-US-236-118

In Study GS-US-236-118, the renal safety of COBI was assessed in HIV-1 infected patients with mild to moderate renal impairment (eGFR 50–89 mL/min) who were switched from ritonavir to COBI while continuing a PI (ATV or DRV) and NRTI backbone through week 96 (N=73).[3-6]

Study Design/Methods

- Phase 3, open-label safety and efficacy study, in which all patients received 1 of 2 treatment regimens:
  - Cohort 1 included ARV treatment-naïve HIV-1 infected adult patients with viral load (VL) ≥1000 copies/mL at screening who received elvitegravir/COBI/FTC/TDF (N=33).
  - Cohort 2 included treatment-experienced HIV-1 infected adults who had a VL <50 copies/mL in the 6 months prior to screening while on a stable regimen of 2 NRTIs plus either ATV/r or DRV/r. These patients switched from ritonavir to COBI while continuing the PI and NRTI backbone (N=73; 70% received TDF).
- The primary renal endpoints included the change from baseline to week 24 in CrCl and creatinine- and cystatin C-based eGFR.[5]
- Data on those treatment-experienced HIV-1 infected adult patients in cohort 2 that switched from ritonavir to COBI are presented below (N=73). **The results were not reported by the individual PI (ATV or DRV) received.**

Results

Select Baseline Characteristics[4-6]

	COBI Switch (N=73)
Age (years), mean	54
Male	82%
Black or African descent	19%
VL (log_{10} c/mL)	1.69
CD4+ count (cells/mm^3), Mean	627
SCr (mg/dL), median (IQR)	1.23 (1.07-1.38)
CrCl (mL/min) by CG, median (IQR)	71 (62-81)
<50 50 to <60 ≥60 to <70 ≥70 to <80 ≥80 to <90	5% 15% 27% 25% 22%
Proteinuria (≥+1)	32%
HIV-associated nephropathy	3%
ATV/r vs DRV/r	71% vs 29%
TDF-containing regimen	51 (70%)

Abbreviations: ATV, atazanavir; CG, Cockcroft-Gault; COBI, cobicistat; CrCl, creatinine clearance; DRV, darunavir; IQR, interquartile range; r, ritonavir; SCr, serum creatinine; TDF, tenofovir disoproxil fumarate; VL, viral load.

Renal Safety-Week 24

- At week 24, no changes in non-creatinine based eGFR (including cystatin C-based eGFR and aGFR) were noted (Table: Changes in eGFR through Week 24).[3]

Changes in eGFR through Week 24[3,4]

	RTV to COBI Switch (N=73)
Changes in eGFR (CG) (n=73)	-3.7 (IQR: -7.4 to 2.0)
Changes in eGFR (CG) by Baseline eGFR:	
≤70 mL/min (n=35)	0.3 (IQR: -5.7 to 5.0)
>70 mL/min (n=38)	-4.1 (IQR: -8.2 to -1.1)
Changes in eGFR (CG) by TDF Use:	
TDF use (n=51)	-3.1 (IQR: -7.6 to 4.0)
Non-TDF (n=22)	-3.8 (IQR: -6.8 to 1.2)
Changes in eGFR (cystatin C) (n=73)	-2.9 (IQR: -7.8 to 2.1)
Abbreviations: CG, Cockcroft-Gault; COBI, cobicistat; eGFR, estimated glomerular filtration rate; IQR, interquartile range; TDF, tenofovir disoproxil fumarate.	

- Through week 24, no change in iohexol clearance-based aGFR [-4.1 (-13.5 to 13.2)] was reported.[4-6]

Renal Safety-Weeks 48 and 96[4-6]

- At weeks 48 and 96, there were minimal changes in CrCl from baseline (Table: Changes in CrCl through Weeks 48 and 96).
- Small changes in CrCl occurred early with stabilization after week 4.
- Patients with lower baseline CrCl (<70 mL/min) did not have greater changes than those with higher CrCl (≥70 mL/min) while receiving COBI.
- No clinically relevant changes in cystatin C-based eGFR were reported through week 96.

Changes in CrCl through Weeks 48 and 96[4-6]

	COBI Switch (N=73)	
	Week 48	Week 96
Changes in CrCl	-3.8 (IQR: -9.0 to 0.8)	-5.0 (IQR: -13.0 to 0.1)
Changes in CrCl by Baseline CrCl:		
<70 mL/min (n=35)	-1.1 (IQR: -6.5 to 6.3)	-3.1 (IQR: -5.1 to 0.5)
≥70 mL/min (n=38)	-6.6 (IQR: -12.4 to -0.7)	-7.6 (IQR: -15.2 to -3.6)
Changes in Cystatin C-based eGFR (n=73)	-4.7 (IQR: -11.7 to 3.9)	-2.8 (IQR: -7.4 to 8.9)
Abbreviations: COBI, cobicistat; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; IQR, interquartile range.		

- Through weeks 48 and 96, no cases of proximal renal tubulopathy were reported.
- At week 48, the percentage of patients that reported a ≥1 grade increase in proteinuria was 14% in those patients with a baseline CrCl <70 mL/min and 11% in those patients with a baseline CrCl ≥70 mL/min at week 48. At week 96, the percentage of patients that reported a ≥1 grade increase in proteinuria was 17% in those patients with a baseline CrCl <70 mL/min and 13% in those patients with a baseline CrCl ≥70 mL/min (Table: Proteinuria by Baseline CrCl through Week 96).[6]

Proteinuria by Baseline CrCl through Week 96[6]

	Baseline CrCl <70 mL/min (n=35)	Baseline CrCl ≥70 mL/min (n=38)
Baseline Proteinuria (≥+1 [grade 1])	43%	21%
Week 48 Proteinuria (≥1 grade increase)	14%	11%
Week 96 Proteinuria (≥1 grade increase)	17%	13%
Abbreviations: CrCl: creatinine clearance.		

Mena et al (2018)[7] conducted an observational, prospective, multicenter cohort study to evaluate the efficacy and safety of switching virologically suppressed HIV-infected patients from DRV/r monotherapy or dual therapy with 3TC to PREZCOBIX monotherapy or dual therapy with 3TC (N=162).

Results

- Select baseline characteristics: mean ± standard deviation (SD) age, 46±12 years; male, 68.5%; PREZCOBIX monotherapy, 43.2%; PREZCOBIX + 3TC, 56.8%.
- After switching, the serum creatinine concentration increased significantly from baseline to week 12 and stabilized thereafter.
  - Eighteen patients had basal eGFR <60 mL/min/1.73 m^2 (mean±SD, 50±6 mL/min/1.73 m^2).
  - The increase in serum creatinine in patients with moderate renal dysfunction was similar to that observed in patients with eGFR >60 mL/min/1.73 m^2 (6.0% and 5.7%, respectively) (Table: Creatinine and eGFR During Follow-up).

Creatinine and eGFR During Follow-up[7]

	Basal[a,b]	Week 24[b]	Week 48[b]	$\Delta_{basal-week48}$[c]	*P*-value
Creatinine (mg/dL)	1.03±0.10	1.09±0.10	1.08±0.14	0.07 (0.04 to 0.10)	<0.001
eGFR (mL/min/1.73 m^2)	87.4±10.2	83.1±9.7	83.8±11.0	-4.0 (-6.3 to -0.9)	<0.001

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; SD, standard deviation. [a]Last determination before switching; [b]Expressed as mean±SD; [c]Change from basal to week 48, expressed with 95% CI.

Vizcarra et al (2019)[8] conducted a phase 4, prospective, single-arm, open-label, cohort study to evaluate the efficacy and safety of switching to a QD regimen of dolutegravir 50 mg plus boosted DRV (PREZCOBIX 800 mg/150 mg [n=29] or DRV/r 800 mg/100 mg [n=22]) in highly treatment-experienced HIV patients with previous VF who were currently virologically suppressed.

Results

- Select baseline characteristics: mean (range) age, 51.6 (33-66) years; male, 71%; mean (range) eGFR, 92.6 (60.9-123.4) mL/min/1.73 m^2; mean (range) urine protein to creatinine ratio (uPCR), 91.1 (15.6-352.3); mean (range) tubular reabsorption of phosphate (TRP), 78.8% (37.9%-90.9%).
- Mean eGFR decreased by 8.8 mL/min/1.73 m^2 (*P*<0.01). The decrease was similar or lower in patients receiving PREZCOBIX vs DRV/r (-7.6 vs -11.9 mL/min/1.73 m^2; *P*=0.24).
  - Overall, mean proteinuria improved from 91.1 to 87.2 mg/dL (*P*=0.86) and mean TRP from 78.8% to 80.1% (*P*=0.8).
  - In patients receiving PREZCOBIX vs DRV/r, the mean percentage change during 48 weeks was -16.93% vs -9.84% for eGFR, -95% vs -76% for uPCR, and 3.08% vs 0.37% for TRP.

Elias et al (2021)[9] reported the results of a retrospective, multicenter study conducted in Spain to estimate the Cr-eGFR changes in patients with HIV starting PREZCOBIX alone or in combination with dolutegravir and/or rilpivirine.

Results

- A total of 725 patients who initiated PREZCOBIX in 21 hospitals across Spain were included.
- In the overall population, a significant decrease from baseline (94.04 mL/min/1.73m^2) was observed in mean Cr-eGFR at week 12 (87.14 mL/min/1.73m^2) and remained stable through week 48 (88.72 mL/min/1.73m^2).

- Factors associated with a Cr-eGFR <60 mL/min/1.73m^2 were age >50 years (adjusted odds ratio [AOR], 10.33; 95% CI, 4.14-25.78; *P*<0.001), female gender (AOR, 2.48; 95% CI, 1.44-4.28; *P*=0.001), acquired immunodeficiency syndrome (AIDS) stage (AOR, 2.61; 95% CI, 1.01-5.06; *P*=0.047), and hepatitis C virus (HCV) coinfection (AOR, 0.43; 95% CI, 0.19-0.96; *P*=0.04).
- Six patients (0.8%) switched the PREZCOBIX-containing regimen due to renal adverse events.
- Higher decreases from baseline in Cr-eGFR were observed with the combination of PREZCOBIX plus rilpivirine and/or dolutegravir than with PREZCOBIX alone at week 12, 24, and 48. See Table: Changes in Cr-eGFR from Baseline through Week 48.
- Decreases in Cr-eGFR ≥15 mL/min/1.73m^2 were observed with higher frequency in patients treated with PREZCOBIX plus rilpivirine and/or dolutegravir than in patients treated with PREZCOBIX alone (Week 12: AOR, 3.23; 95% CI, 1.34-7.78; *P*=0.009; Week 24: AOR, 2.93; 95% CI, 1.59-5.42; *P*=0.001; Week 48: AOR, 2.43; 95% CI, 1.07-5.50; *P*=0.033).

Changes in Cr-eGFR from Baseline through Week 48[9]

	PREZCOBIX	PREZCOBIX with rilpivirine and/or dolutegravir	Adjusted *P*-value
Cr-eGFR, mL/min/1.73m^2			
Baseline	94.49	91.28	-
Week 12	88.36	81.55	0.044
Week 24	90.42	83.31	0.026
Week 48	89.61	82.68	0.005
Abbreviations: Cr-eGFR, creatinine estimated glomerular filtration rate.			

DRV/COBI/FTC/TAF STR DATA

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 ARV treatment-naïve HIV-1-infected adults (N=725).[10]

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

- The mean change (increase) in $eGFR_{cyst}$ (CKD-EPI formula) at week 48 was greater for the STR (5.3 mL/min/1.73 m²) than PREZCOBIX + FTC/TDF (2.9 mL/min/1.73 m²) (*P*=0.001).
- The increase in serum creatinine at week 48 was less for the STR (+4.8 µmol/L) than PREZCOBIX + FTC/TDF (+8.2 µmol/L) (*P*<0.0001).

- The mean change (decrease) in eGFR based on serum creatinine ($eGFR_{cr}$; CKD-EPI formula) at week 48 was less for the STR (-5.9 mL/min/1.73 m²) than PREZCOBIX + FTC/TDF (-9.3 mL/min/1.73 m²) (*P*<0.0001).
- No clinically relevant changes in eGFR occurred through week 96 in the STR arm or PREZCOBIX + FTC/TDF arm. In the STR arm[15]:
    - The median change (decrease) in eGFR based on Scr 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 estimated glomerular filtration rate based on cystatin C ($eGFR_{cyst}$) at week 84 was 3.2 mL/min/1.73 m².
- At week 48, measures of proteinuria improved for the STR vs. PREZCOBIX + FTC/TDF, as measured 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 vs. -0.58 mg/g, *P*=0.003), retinol binding protein/creatinine ratio (16.84 vs. 401.12 µg/g, *P*<0.0001), and β-2-microglobulin/creatinine ratio (-100.58 vs. 837.63 µg/g, *P*<0.0001).
- Improvements in proteinuria were maintained through week 96 in the STR arm vs PREZCOBIX + FTC/TDF arm (week 48 data), 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.[15]
- Renal adverse events (AEs) regardless of causality occurred in 2% (7/362) of the STR patients and in 6% (21/363) of PREZCOBIX + FTC/TDF patients through week 48.
- At week 96, renal AEs regardless of causality occurred in 5% (17/362) of patients in the STR arm, with dysuria (n=4), hematuria (n=3), renal colic and urethral discharge (each n=2) occurring in ≥2 patients.[15]
- There were no discontinuations due to renal AEs and no renal AEs were suggestive of treatment-emergent proximal renal tubulopathy or Fanconi syndrome in either treatment group through week 96.
- Improvements in renal function were similar between subgroups.[16]
- Rates of renal AEs of interest (clinical events, laboratory-related events) were similar between the STR and PREZCOBIX + FTC/TDF arms across genders.[17]

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 TDF/FTC in virologically-suppressed, HIV-1-infected adults (N=1141).[11]

Study Design/Methods

- Patients were stratified according to bPI (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.[18]

Results

- From baseline to week 48, $eGFR_{cyst}$ was stable in the STR arm (mean change -0.4 mL/min/1.73 m^2, *P*=0.24) and decreased in the PREZCOBIX + FTC/TDF group (mean change -1.9 mL/min/1.73 m^2, *P*=0.0007 vs. baseline, *P*=0.034 for between-treatment comparison at week 48).

- Median changes in $eGFR_{cyst}$ were similar through week 96.[18]
- Increases in serum creatinine were larger for the STR arm vs. the bPI arm (1.3 vs. 0.6 μmol/L; not significant).
- Decreases in $eGFR_{cr}$ were larger for the STR arm vs. the bPI arm (-1.9 vs. -0.9 mL/min/1.73 m^2; not significant).
  - From baseline to week 96 the median change in $eGFR_{cr}$ in the STR arm was -1.3 mL/min/1.73 m^2.[18]
- In patients who received PREZCOBIX + FTC/TDF (98 in the STR arm and 64 in the bPI arm and who had this as the screening regimen), serum creatinine decreased in the STR arm and increased for the bPI arm, $eGFR_{cr}$ increased in the STR arm and decreased in the bPI arm, and $eGFR_{cyst}$ increased in the STR arm and decreased in the bPI arm.
- In patients who started with DRV/r + FTC/TDF (439 in the STR arm and 202 in the bPI arm), patients in the STR arm had larger increases in serum creatinine and decreases in $eGFR_{cr}$ and fewer decreases in $eGFR_{cyst}$ than those in the bPI arm.
- Compared with staying on the bPI arm, switching to the STR arm resulted in significant improvements at 48 weeks in all measures of quantitative proteinuria (both glomerular proteinuria and proximal tubular proteins, $P<0.0001$ for all measures), including mean changes in the urine protein/creatinine ratio (-33.90 mg/g in the STR arm vs. -6.43 mg/g in the bPI arm), urine albumin/creatinine ratio (-3.20 vs. 1.25 mg/g), urine retinol binding protein/creatinine ratio (-630.45 vs. 1037.06 μg/g), and urine β-2-microglobulin/creatinine ratio (-1454.70 vs. 1371.29 μg/g).
- In the STRarm, similar improvements in renal biomarkers were maintained through week 96.[18]
- Renal AEs occurred in 30/763 (4%) and 18/378 (5%) patients in the STR and bPI arms, respectively through week 48.
  - Three AEs led to study discontinuation, 1 in the STR arm (grade 2 non-serious worsening of pre-existing chronic kidney disease) and 2 in the bPI arm (1 grade 4 non-serious toxic nephropathy and 1 grade 1 non-serious renal tubular disorder related to TDF).
  - No renal AEs suggested treatment-emergent proximal renal tubulopathy in the study group.
- Improvements in renal function were observed regardless of age, gender, or race.[19]
- Overall incidences of renal AEs of interest (clinical events, laboratory-related events) were similar across genders.[17]

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).[12]

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

- The mean change in serum creatinine from baseline at week 48 was 0.06 mg/dL (95% CI, 0.04-0.08) for the TAF group and 0.09 mg/dL (95% CI, 0.05-0.14) for the TDF group ($P=0.053$).
  - Serum creatinine increased as early as week 2, but then remained stable throughout the study period.

- The increase from baseline to week 48 in urine retinol binding protein/creatinine ratio was smaller for the TAF group vs. the TDF group (median percent change: TAF 9%, TDF 54%, *P*=0.003).
- From baseline to week 48, the urine β-2-microglobulin/creatinine ratio decreased for the TAF group and slightly increased for the TDF group (median percent change: TAF -42.0% vs. TDF 2.3%, *P*=0.002).
- There were no significant differences between groups in changes from baseline for urine albumin/creatinine or urine protein/creatinine ratios, fractional excretion of uric acid or phosphate, or treatment-emergent dipstick proteinuria.
- One patient in the TDF group experienced proximal renal tubulopathy which led to discontinuation.

Renal Parameters[12]

Renal Parameters	TAF (n=103)	TDF (n=50)	*P*-value
Estimated glomerular filtration rate (mL/min; Cockroft Gault)	-2.9 mL/min	-10.6 mL/min	0.017
Treatment emergent dipstick proteinuria[a]	33, (32%)	17, (34%)	0.98
Urinary albumin/creatinine (mg/g)[b]	-13.1%	-22.6%	0.17
Urinary protein/creatinine (mg/g)[b]	-8.22%	-27.52%	0.19
Fractional excretion of phosphate (%)[c]	2.4	1.8	0.85
Fractional excretion of uric acid (%)[c]	0.2	-0.2	0.79

Abbreviations: TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
2-sided Wilcoxon rank sum text to compare % change in median from baseline between the 2 treatment groups.
[a]Analysis of covariance adjusting for baseline toxicity grade of proteinuria.
[b]Median % change.
[c]Median change.

Heron et al (2020)[20] published a case report of a 46-year-old male patient receiving the STR DRV/COBI/FTC/TAF for HIV who developed proximal tubulopathy when treated with gentamicin for febrile neutropenia in the context of relapsed Hodgkin lymphoma.

- At presentation, his blood chemistry was within normal limits.
- The patient was started on piperacillin, tazobactam, and gentamicin for febrile neutropenia. He received two daily doses of gentamicin at 3.8 mg/kg. Sepsis and hypotension persisted, and on day 4 he received a 3rd dose of gentamicin at 5.8 mg/kg.
- Hypophosphatemia and hypokalemia were noted within 24 hours of receiving gentamicin. Proteinuria with urinary protein creatinine ratio of 162.5 mg/mmol creatinine, and glycosuria with urine glucose concentration of 107 mmol/L were also noted. Renal proximal tubulopathy was suspected and gentamicin was discontinued.
- The patient's serum and urine biochemistry were within normal ranges 11 days after discontinuation of gentamicin. Given the patient's improvement, DRV/COBI/FTC/TAF was not discontinued.

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 10 April 2023.

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