PREZCOBIX® (darunavir/cobicistat)
Use of PREZCOBIX in Patients with Renal Impairment

SUMMARY

- There is no data on the use of PREZCOBIX in patients receiving peritoneal dialysis or continuous renal replacement therapy (CRRT).
- In Gilead Study 118, the renal safety of cobicistat (COBI) was assessed in HIV-1 infected patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 50–89 mL/min) who were switched from ritonavir (RTV) to COBI while continuing a PI (atazanavir [ATV] or darunavir [DRV]) and NRTI backbone through week 96 (N=73).[1–4]
  - **The results were not reported by the individual PI (ATV or DRV) received.**
  - The majority of patients (51/73) received tenofovir disoproxil fumarate (TDF) as part of the NRTI backbone.[3]
  - In those patients that switched from RTV to COBI, 89% (snapshot analysis) reported virologic response (viral load [VL] <50 copies/mL) and no development of viral resistance was reported at week 96 (n=54).[4]
  - At week 96, minimal changes in creatinine clearance (CrCl) from baseline were reported.[4]
  - Through week 96, no cases of proximal renal tubulopathy were reported.[4]
  - Common adverse events (AEs) ≥10% (all grades) included upper respiratory tract infection (21%), nasopharyngitis (19%), diarrhea (14%), bronchitis (14%), headache (14%), nausea (12%), arthralgia (12%), hyperbilirubinemia (11%), and influenza (11%; occurred in subjects on ATV + COBI + 2 NRTIs).[4]
- In a case report of a patient with HIV and renal dysfunction on hemodialysis, trough concentrations of darunavir and cobicistat did not differ between days with and without hemodialysis. The patient maintained viral suppression and no adverse events were reported.[5]

PHASE 3 STUDY

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 RTV to COBI while continuing the PI (ATV or DRV) and NRTI backbone through week 96 (N=73).[1–4]

Study Design/Methods

- Ongoing 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 VL ≥1000 copies/mL at screening who received elvitegravir/COBI/emtricitabine (FTC)/TDF.
  - 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/RTV or DRV/RTV. These patients switched from RTV to COBI while continuing the PI and NRTI backbone (N=73).
- The primary renal endpoints included the change from baseline to week 24 in CrCl and creatinine- and cystatin C-based eGFR.[3]
- The primary efficacy endpoint is VL <50 copies/mL at week 24 (snapshot analysis).[3]
- Secondary efficacy endpoints include VL <50 copies/mL at week 48 (snapshot analysis), VL <50 copies/mL (missing=failure and missing=excluded), and the change from baseline in CD4+ count.[3]
  - The focus of this review will include those treatment-experienced HIV-1 infected adult patients in cohort 2 that switched from RTV to COBI (N=73). **The results were not reported by the individual PI (ATV or DRV) received.**

Results

Baseline Characteristics

- Forty-seven percent of patients had CrCl between 50-70 mL/min.[2]
- The majority of patients (51/73) received TDF.[3]

Select Baseline Characteristics[2–4]

	RTV to 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) CG, Median (IQR)	71
<50	5%
50 to <60	15%
≥60 to <70	27%
≥70 to <80	25%
≥80 to <90	22%
≥90	5%
Proteinuria (≥+1)	32%
HIV-associated nephropathy	3%
TDF-containing regimen	51 (70%)

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

Efficacy

- High rates of virologic suppression and no development of viral resistance to any components of the PI + COBI containing treatment regimen were reported at weeks 48 and 96 (Table: Viral Load <50 copies/mL at Weeks 24, 48, and 96).[2–4]

Viral Load <50 copies/mL at Weeks 24, 48, and 96[1–4]

	RTV to COBI Switch		
	Week 24 (N=73)	Week 48 (N=73)	Week 96 (n=54)[a]
Snapshot analyses (ITT)	90%	82%[b]	89%[c]
Missing Failure (ITT)	95%	88%	96%
Missing Excluded	100%	97%	96%

Abbreviations: COBI, cobicistat; ITT, intention-to-treat; RTV, ritonavir.
[a]The analysis set included 2 subjects who completed 48 weeks of treatment and consented for protocol amendment 2, where subjects were followed up for an additional 48 weeks; [b]Two subjects had virologic failure (viral load ≥50 copies/mL) at week 48, 5 subjects discontinued due to adverse events, and 6 subjects were suppressed prior to study drug discontinuation due to other reasons; [c]Two subjects had virologic failure (viral load ≥50 copies/mL) at week 96 (1 with 79 c/mL [resuppressed at week 108] and the other with 56 c/mL at last available visit), 2 subjects discontinued due to adverse events, and 2 subjects were suppressed prior to study drug discontinuation for other reasons.

Safety

Renal Safety-Week 24

- At week 24, no changes in noncreatinine based eGFR (including cystatin C-based eGFR and actual glomerular filtration rate [GFR]) were noted (Table: Changes in eGFR through Week 24).[1]

Changes in eGFR through Week 24[1,2]

	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); >70 mL/min (n=38)	0.3 (IQR: -5.7 to 5.0)-4.1 (IQR: -8.2 to -1.1)
Changes in eGFR (CG) by TDF Use:	
TDF use (n=51); non-TDF use (n=22)	-3.1 (IQR: -7.6 to 4.0)-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; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.	

- Through week 24, no change in iohexol clearance-based actual GFR [-4.1 (-13.5 to 13.2)] was reported.[2–4]

Renal Safety-Week 48 and Week 96[2–4]

- At weeks 48 and 96, there were minimal changes in CrCl from baseline reported (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 weeks 48 and 96.

Changes in CrCl through Weeks 48 and 96[2–4]

	RTV to 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) ≥70 mL/min (n=38)	-1.1 (IQR: -6.5 to 6.3) -6.6 (IQR: -12.4 to -0.7)	-3.1 (IQR: -5.1 to 0.5) -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; RTV, ritonavir.		

- 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).[4]

Proteinuria by Baseline CrCl through Week 96[4]

	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.		

Adverse Events

- At week 96, common AEs ≥10% (all grades) included upper respiratory tract infection (21%), nasopharyngitis (19%), diarrhea (14%), bronchitis (14%), headache (14%), nausea (12%), arthralgia (12%), influenza (11%), and hyperbilirubinemia (11%; all in subjects on ATV).[4]
  - At week 48, common AEs ≥10% (all grades) included upper respiratory tract infections (19%), nasopharyngitis (12%), nausea (12%), diarrhea (11%), headache (11%), and hyperbilirubinemia (11%; occurred in subjects on ATV + COBI + 2 NRTIs).[2,3]
  - At week 24, serious AEs were reported in 5% (n=4) patients which included acute myocardial infarction (1%), suicidal ideation (1%), nephrolithiasis (1%), and angioedema (1%).[1,3]
- AEs leading to treatment discontinuation included headache (n=2) and nausea (n=2) through weeks 48 and 96.[2–4]

Kobayashi et al (2021)[5] published a case report of a male patient in his 40s with HIV and end-stage renal disease (ESRD) on hemodialysis who was maintained on PREZCOBIX + doravirine.

- Prior to progression to ESRD, the patient had been virologically suppressed for more than 1 year on raltegravir plus PREZCOBIX.
- Viral rebound (HIV RNA of 3,480 copies/mL) was later reported and was attributed to a drug interaction with raltegravir and calcium polystyrene sulfonate.
- The patient was then switched to doravirine 100 mg plus PREZCOBIX once daily after breakfast, and viral suppression was rapidly achieved to undetectable levels.
- His renal failure progressed, and he was started on maintenance hemodialysis for 4 hours three times a week.
- Drug concentrations were measured during hemodialysis at different timepoints on days 47, 54, and 82. See Table: Mean Drug Concentrations During Hemodialysis.
  - The trough concentrations of darunavir and cobicistat did not differ between days with and without hemodialysis. Significantly higher concentrations were observed after hemodialysis and were attributed to hemoconcentration.
- Viral suppression was maintained through day 111 with no reported adverse events.

Mean Drug Concentrations During Hemodialysis[5]

Timepoints	**Concentration Median ± SD**		
	Doravirine	**Darunavir**	**Cobicistat**
A: Trough on day of HD	5,839 ± 283 nM	9,528 ± 2,101	99 ± 28
P-value for A vs D	**0.046**	0.44	0.96
B: Before HD (1 hour after medication)	5,743 ± 187 nM	6,657 ± 1,715	40 ± 8
P-value for B vs C	0.065	**0.027**	**0.016**
C: After HD (5 hours after medication)	5,480 ± 333 nM	27,265 ± 6,976	1,826 ±338
P-value for C vs D	0.43	**0.034**	**0.019**
D: Trough on the day after HD	5,482 ± 226 nM	9,552 ± 1,575	121 ± 23
Abbreviations: HD, hemodialysis; SD, standard deviation. Statistical analyses were performed with the paired t-test.			

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 30 October 2023.

REFERENCES

1. Post F, Winston J, Andrade-Villanueva J, et al. Elvitegravir/cobicistat/tenofovir DF/emtricitabine (STB) and cobicistat (COBI) in HIV infected patients with mild to moderate renal impairment. Poster presented at: the 7th IAS Conference on HIV Pathogenesis, Treatment, and Prevention; June 30-July 3, 2013; Kuala Lampur, Malaysia.

2. McDonald C, Martorell C, Ramgopal M, et al. Switching from ritonavir (RTV) to cobicistat (COBI) in HIV patients with renal impairment who are virologically suppressed on a protease inhibitor based regimen. Poster presented at: 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 5-9, 2014; Washington, DC.

3. McDonald CK, Martorell C, Ramgopal M, et al. Cobicistat-boosted protease inhibitors in HIV-infected patients with mild to moderate renal impairment. *HIV Clin Trials*. 2014;15(6):269-273.

4. Fisher M, McDonald C, Moyle G, et al. Cobicistat (COBI) in HIV-infected patients with mild to moderate renal impairment. Poster presented at: HIV Drug Therapy Glasgow 2014; November 2-6, 2014; Glasgow, UK.

5. Kobayashi M, Chinen M, Hirano A, et al. Successful treatment by doravirine with cobicistat-boosted darunavir for end-stage renal failure under chronic haemodialysis. *J Antimicrob Chemoth*. 2021;76(5):1370-1372.