SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
Safety Information of SYMTUZA– Renal Effects

SUMMARY

- In the AMBER study, 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 SYMTUZA (5.3 mL/min/1.73 m²) than control (2.9 mL/min/1.73 m²) (*P*=0.001).[1]
- In the EMERALD study, increases in serum creatinine were larger for SYMTUZA vs. boosted protease inhibitor (bPI; 1.3 vs. 0.6 μmol/L; not significant).[2]
- In the DIAMOND study, there were no discontinuations due to renal adverse events (AEs).[3]
- 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 tenofovir alafenamide (TAF) group and 0.09 mg/dL (95% CI, 0.05-0.14) for the tenofovir disoproxil fumarate (TDF) group (*P*=0.053).[4]
- A case of renal proximal tubulopathy was reported in HIV-infected patient with a history of Hodgkin lymphoma on a stable antiretroviral (ARV) regimen of TAF, emtricitabine (FTC), darunavir (DRV), and cobicistat (COBI) and gentamicin therapy.[5]

CLINICAL STUDIES

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 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 CD4+ 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 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.

Results

- The mean change (increase) in $eGFR_{cyst}$ (CKD-EPI formula) at week 48 was greater for SYMTUZA (5.3 mL/min/1.73 m²) than control (2.9 mL/min/1.73 m²) (*P*=0.001).
- The increase in serum creatinine at week 48 was less for SYMTUZA (+4.8 μmol/L) than control (+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 SYMTUZA (-5.9 mL/min/1.73 m²) than control (-9.3 mL/min/1.73 m²) (*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.[6] In the SYMTUZA arm[7]:
    - 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 SYMTUZA vs. control, 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 SYMTUZA arm vs control 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.[7] Results were consistent across subgroups.[6]
- Renal AEs regardless of causality occurred in 2% (7/362) of SYMTUZA patients and in 6% (21/363) of control patients through week 48.
- 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.[7]
- 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.[8]
- Rates of renal AEs of interest (clinical events, laboratory-related events) were similar between SYMTUZA and control across genders.[9]

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 TDF/FTC in virologically-suppressed, HIV-1-infected adults (N=1141).[2]

Study Design/Methods

- Patients were stratified according to bPI (DRV/ritonavir [r] or DRV/COBI QD, atazanavir [ATV]/r or ATV/COBI QD, or lopinavir [LPV]/r BID) and then randomized 2:1 to switch to SYMTUZA or to continue their bPI regimen.

Results

- From baseline to week 48, $eGFR_{cyst}$ was stable in the SYMTUZA arm (mean change -0.4 mL/min/1.73 m^2, $P=0.24$) and decreased in the control 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.[10]
  - In the SYMTUZA arm, median changes in $eGFR_{cyst}$ were stable (range: -2 to +2 mL/min/1.73m^2) through week 96 across the subgroups of age, gender, race, screening bPI, and screening boosting agent.[6]
- Increases in serum creatinine were larger for SYMTUZA vs. bPI (1.3 vs. 0.6 μmol/L; not significant).
- Decreases in $eGFR_{cr}$ were larger for SYMTUZA vs. bPI (-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 SYMTUZA arm was -1.3 mL/min/1.73 m^2.[10]
- In patients who received DRV/COBI + FTC/TDF (98 in the SYMTUZA arm and 64 in the bPI arm and who had this as the screening regimen), serum creatinine decreased in the SYMTUZA arm and increased for the bPI arm, $eGFR_{cr}$ increased in the SYMTUZA arm and decreased in the bPI arm, and $eGFR_{cyst}$ increased in the SYMTUZA arm and decreased in the bPI arm.
- In patients who started with DRV/r + FTC/TDF (439 in the SYMTUZA arm and 202 in the bPI arm), patients in the SYMTUZA 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 SYMTUZA 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 SYMTUZA 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).
    - Proteinuria markers continued to improve through week 96 and similar results were observed across the subgroups of age, gender, and race.[6]
- In the SYMTUZA arm, similar improvements in renal biomarkers were maintained through week 96.[10]
- Renal AEs occurred in 30/763 (4%) and 18/378 (5%) patients in the SYMTUZA and bPI arms, respectively through week 48.
    - Three AEs led to study discontinuation, 1 in the SYMTUZA 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 or Fanconi syndrome through Week 96.[6]
- Improvements in renal function were observed regardless of age, gender, or race.[11]
- Overall incidences of renal AEs of interest (clinical events, laboratory-related events) were similar across genders.[9]

DIAMOND

The DIAMOND study is a phase 3, single-arm, open-label, multicenter study to evaluate the safety and efficacy of SYMTUZA in newly diagnosed, HIV-1 infected, treatment-naïve patients in a rapid initiation model of care over 48 weeks (N=109).[3]

Study Design/Methods

- Eligible patients were enrolled and started on a STR consisting of SYMTUZA (DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg) orally once daily within 24 hours of the screening/baseline visit and before results of the baseline safety and resistance laboratory tests were available.

Results

- There were no discontinuations due to renal AEs.

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).[4]

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 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[4]

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.

PUBLISHED CASE REPORT

Heron et al (2020)[5] described a case report of renal proximal tubulopathy in a 46-year patient with a history of HIV and Hodgkin lymphoma on a stable ARV regimen of TAF 10 mg QD, FTC, DRV, and COBI and gentamicin therapy for febrile neutropenia.

- The patient was receiving treatment consisting of dexamethasone, cytarabine and carboplatin for relapsed Hodgkin lymphoma.
- Eighteen days after starting chemotherapy, the patient presented to the hospital with febrile neutropenia.
- Serum creatinine was 82 µmol/L (reference range: 60-110 µmol/L) with an eGFR of >90 mL/min/1.73m^2. Serum potassium and serum phosphate were within normal limits.
- The patient was started on piperacillin, tazobactam, and gentamicin for febrile neutropenia. Gentamicin was dosed at 3.8 mg/kg two times a day with a third dose on day 4 at 5.8 mg/kg.
- Within 24 hours of receiving gentamicin, the patient developed hypophosphatemia for 11 days and hypokalemia for 7 days.
    - Urinary potassium concentration was 24 mmol/L with a fractional excretion of 21.5%, and urinary phosphate concentration was 8 mmol/L with a fractional excretion of 60.4%.
- The patient also presented with proteinuria, with a urinary protein to creatinine ratio of 162.5 mg/mmol creatinine and glycosuria, with a urine glucose concertation of 107 mmol/L.

- The patient was diagnosed with renal proximal tubulopathy and gentamicin was discontinued. Eleven days after discontinuing gentamicin, urinary electrolyte wasting and proteinuria improved and glycosuria resolved.
- The patient continued treatment for relapsed Hodgkin lymphoma with no changes in ARV therapy.

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 12 September 2023.

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