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Title Page:

Full Title: Elvitegravir/cobicistat/emtricitabine/tenofovir DF in HIV-Infected Patients with Mild to Moderate Renal Impairment

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Running Head: Elvitegravir/cobicistat/emtricitabine/tenofovir DF in Renal Impairment

Abstract:

In HIV-1 infected treatment- naïve patients with mild to moderate renal impairment (creatinine clearance [CrCl]: 50-89 mL/min), elvitegravir/cobicistat/emtricitabine/tenofovir DF (STB, n=33) achieved high rates of virologic success [78.8%; 95% CI: 61.1% to 91.0%] and was well tolerated through Week 48. Four patients discontinued study drug due to an adverse event, none due to proximal renal tubulopathy. As expected, decreases in CrCl were noted as early as Week 2, after which they stabilized. The renal safety profile of STB in patients from this study is consistent with the long-term experience in a large number of patients with CrCl ≥ 70 mL/min.

Key Words:

Renal Impairment, HIV, elvitegravir/cobicistat/emtricitabine/tenofovir DF, Renal Safety

Introduction:

Elvitegravir/cobicistat/emtricitabine/tenofovir DF (EVG/COBI/FTC/TDF, STB) was approved as the first single-tablet regimen containing an HIV-1 integrase strand transfer inhibitor, and is recommended by treatment guidelines. [1,2] The two Phase 3 studies, which formed the basis for the approval of STB, were conducted in treatment naïve patients with creatinine clearance (CrCl) ≥ 70 mL/min using the Cockcroft-Gault method.[3,4] This CrCl threshold was set with consideration for the expected COBI-associated decrease in CrCl due to its inhibition of creatinine secretion and the impracticality of dose adjustment for FTC and TDF within STB when CrCl declines below 50 mL/min. EVG and COBI are eliminated mainly via hepatic metabolism,[5,6] and FTC and TDF can be used without dose adjustment in patients with CrCl ≥ 50 mL/min,[7,8] thus, a scientific rationale exists to evaluate STB in HIV-1 infected treatment naïve patients with CrCl ≥ 50 mL/min. We present in this report the safety and efficacy of STB in

treatment naïve patients with mild to moderate renal impairment (CrCl 50 to 89 mL/min) through Week 48.

Methods:

Study Design and Patients

Study GS-US-236-0118 is a 96-week, phase 3, open-label, multicenter, two cohort study to evaluate the safety and efficacy of COBI-containing regimens in HIV-1 infected adult patients who are either treatment-naïve (STB cohort) or treatment-experienced (COBI cohort: switch ritonavir to COBI) with stable, mild to moderate renal impairment. As the two cohorts are distinct and not comparable (treatment-naïve versus –experienced), only the STB cohort (treatment naïve patients) is presented in this report. Eligibility criteria included no prior use of antiretroviral agents, HIV-1 RNA ≥ 1000 copies/mL regardless of CD4 cell count, genotype showing sensitivity to FTC and TDF, and stable renal function as determined by the investigator, with CrCl 50 to 89 mL/min for at least 6 months prior to the screening visit. The study was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by central or site-specific institutional review boards or ethics committees. All participants gave written informed consent.

Procedures

Laboratory analyses (hematology, urinalysis and chemistry), including HIV-1 RNA and CD4 cell count, estimation of CrCl, and complete or symptom-directed physical examinations were performed at screening, baseline, and all subsequent study visits. Patients returned for study visits at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48. Following a confirmed virologic rebound (HIV-1 RNA ≥400 copies/mL or > 1 $\log_{10}$ increase from nadir) or confirmed suboptimal virologic response (HIV-1 RNA ≥ 50 copies/mL and < 1 $\log_{10}$ reduction from baseline by Week

8), confirmatory samples were sent for HIV-1 genotype and phenotype testing against protease, reverse transcriptase and integrase using PhenoSense GT, PhenoSense Integrase, and GeneSeq Integrase assays (Monogram Biosciences). The renal criterion for potential study drug discontinuation was CrCl < 50 mL/min confirmed within 7 days, and > 20% decrease in cystatin C-based estimated GFR (eGFR) at the confirming visit. The use of the latter is to have an assessment of eGFR that is not affected by inhibition of renal tubular creatinine secretion by COBI.

Statistical Analysis

Efficacy assessments included all patients who received at least 1 dose of study drug. The primary efficacy endpoint was the percentage of patients with HIV-1 RNA < 50 copies/mL at Week 24 as defined by the Food and Drug Administration (FDA) snapshot analysis algorithm; the percentage of patients and the associated 95% confidence intervals (CIs) were determined. Secondary efficacy endpoints included: the percentage of patients with HIV-1 RNA < 50 copies/mL at Week 48 by snapshot, missing = failure, and missing = excluded, and the change from baseline in CD4 cell count.

Safety assessments were summarized for the safety analysis set, which included all patients who received at least 1 dose of study drug. Selected safety endpoints were summarized by baseline CrCl (< 70 mL/min and ≥70 mL/min). The primary renal endpoints included the change from baseline at Week 24 in the following parameters: CrCl; eGFR using Modification of Diet in Renal Disease (MDRD);[9] and eGFR using chronic kidney disease epidemiology collaboration (CKD-EPI) methods based on serum creatinine or cystatin C (adjusted for age, sex, and race).[10,11]

The laboratory definition of proximal renal tubulopathy (PRT) was as follows: more than one confirmed concurrent new or worsening renal abnormalities (increase in serum creatinine > 0.4 mg/dL, hypophosphatemia, proteinuria [by dipstick], normoglycemic glycosuria) through Week 48.

These endpoints, and other safety assessments, were summarized using descriptive statistics. Adverse events (AEs) and any laboratory abnormalities recorded as AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0.

This study is registered with clinicaltrials.gov, number NCT01363011.

Results:

Of the 71 screened patients, 33 were enrolled and received at least 1 dose of STB. The median duration of exposure to study drug was 61 weeks (Q1 to Q3: 58 to 72 weeks). The baseline characteristics are shown in Table 1. Through Week 48, 6 of 33 patients (18%) discontinued study drug: the reasons included AEs (n=4), investigator's discretion (n=1), and withdrawal of consent (n=1).

STB achieved a high rate of virologic success (HIV-1 RNA < 50 copies/mL) by FDA snapshot analysis at Week 24 [84.8% (28/33); 95% CI: 68.1% to 94.9%] and at Week 48 [78.8% (26/33); 95% CI: 61.1% to 91.0%]. The percentage of patients with HIV-1 RNA < 50 copies/mL at Week 48 were 84.8% (28/33 patients; missing = failure) and 93.3% (28/30 patients; missing = excluded). The mean (SD) increase in CD4 cell count from baseline at Week 48 was 273 (183.5) cells/μL. Two patients who met the protocol-defined criterion for resistance testing were analyzed and neither developed resistance to any components of STB.

The overall safety findings were generally consistent with those of the Phase 3 studies. No treatment-emergent deaths were reported. Serious AEs were reported for 12% of patients (n=4): increased blood creatine phosphokinase (n=1); infected cyst (n=1); right ventricular failure and

lymphoma (both in the same patient; n=1); hepatitis C and Hodgkin's disease (both in the same patient; n=1). None were considered related to study drug except for the serious AE of increased blood creatinine phosphokinase. The most frequent AEs were diarrhea (30%); insomnia (21%); and nausea and headache (each 18%). AEs considered related to study drug by the investigator were reported for 45% of subjects (15/33 subjects). The most frequently reported AEs considered related to study drug by the investigator were nausea (3 patients), and blurred vision, upper abdominal pain, vomiting, decreased glomerular filtration rate, hyperglycemia, headache, and insomnia (each reported for 2 patients).

Four patients (12%) discontinued study drug due to an AE. One patient discontinued due to hepatitis C and Hodgkin's disease. The other three patients discontinued due to renal AEs, two of whom met the protocol-defined criterion for potential discontinuation. All three patients had baseline CrCl between 50-55 mL/min and developed CrCL < 50mL/min without evidence of PRT. Only one patient had cystatin C-based eGFR < 50 mL/min/1.73m^2 at the time of discontinuation, which was pre-existing at baseline. CrCl returned to baseline after STB discontinuation in two patients; one patient did not have any post discontinuation data available.

Increases in median values for serum creatinine were noted as early as Week 2 (0.16 mg/dL [IQR: 0.10 to 0.23]), after which they generally stabilized and were nonprogressive through Week 48 (0.17 mg/dL [IQR: 0.08 to 0.26]) (Figure 1a). Corresponding decreases in CrCl were also noted at Week 2 (-8.9 mL/min [IQR: -11.3 to -5.8]) and through Week 48 (-7.6 mL/min [IQR: -12.2 to -2.2]). The median changes in other creatinine-based eGFR endpoints at Week 48 were consistent with that for CrCl ($eGFR_{MDRD}$: -12.1 mL/min/1.73m^2 and $eGFR_{CKD\text{-}EPI,\ creatinine}$: -13.1 mL/min/1.73m^2). There was no change in cystatin C-based eGFR from baseline (median 76.9 mL/min/1.73m^2 [IQR: 61.7 to 90.1]) to Week 48 (median change +1.6 mL/min/1.73m^2

[IQR: -8.0 to 6.9]). The changes from baseline at Week 48 in median values for CrCl were similar for patients in subgroups by baseline CrCl (Figure 1b). One patient had confirmed increase in serum creatinine > 0.4 mg/dL but no tubular abnormalities, and discontinued study drug due to renal AE. No patient met the laboratory definition of PRT. Three patients had confirmed new or worsening proteinuria (by dipstick), which improved while continuing study drug.

Discussion:

This is the first study evaluating the efficacy and safety of STB in treatment naïve patients with mild to moderate renal impairment, who are considered to be at increased risk from a renal safety perspective. In these patients, STB achieved high rates of virologic suppression and was well tolerated with no new renal safety signals.

FTC and TDF, the two nucleos(t)ide reverse transcriptase inhibitors within STB, require dose adjustment in patients with CrCl < 50 mL/min.[12] However, EVG and COBI do not require dose adjustment in patients with renal impairment as they are primarily eliminated via hepatic metabolism. In a phase 1 study of EVG and COBI in patients with severe renal impairment (CrCl < 30 mL/min), no clinically relevant differences in EVG or COBI exposures were seen.[13] Importantly, the expected decrease in CrCl due to COBI resulted in the recommendation for initiating STB only in patients with CrCl ≥ 70 mL/min.

It is reassuring that no new or unexpected safety signals of STB were observed through 48 weeks in treatment naïve patients with mild to moderate renal impairment. STB was generally well tolerated and the safety findings were consistent with those observed in two large phase 3 registrational studies.[3,4]

Similar to patients in the phase 3 studies of COBI-containing regimens (i.e. STB or COBI-boosted atazanavir + FTC/TDF) with CrCl ≥ 70 mL/min,[3,4,14] those in this study had nonprogressive decreases in CrCl and no notable changes in cystatin C-based eGFR. Importantly, the changes in CrCl in patients with baseline CrCl < 70 mL/min were similar to those in patients with baseline CrCl ≥ 70 mL/min. The renal AEs that led to study drug discontinuation were generally consistent with the effects of COBI on serum creatinine, and none of the patients had laboratory findings indicative of PRT.

Despite the relatively small sample size, the strength of our study is the comprehensive assessment of renal safety in treatment naïve patients who were otherwise not eligible to initiate STB per the current prescribing recommendation due to low CrCl (i.e. 50 to < 70 mL/min).

In this first study of STB in treatment naïve patients with mild to moderate renal impairment, STB was generally safe, well tolerated and efficacious. Thus, the use of STB can be considered in treatment naïve patients with mild to moderate renal impairment with careful monitoring of renal function.

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Table 1. Baseline Characteristics

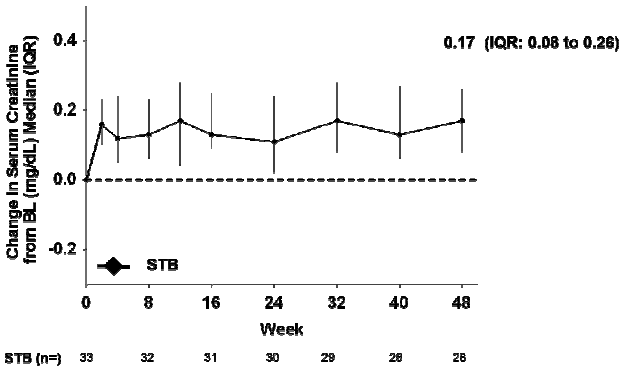
	STB (n=33)
Age (years), Mean (SD)	50 (12)
Male	82%
Black or African Descent	39%
HIV-1 RNA (log10c/mL), Median	4.73 (4.45, 5.17)
CD4 count (cells/mm3), Mean (SD)	356 (174)
Background TDF	100%
Serum Cr (mg/dL), Median (IQR)	1.12 (0.99 to 1.29)
CrCl (mL/min), Median (IQR)	73 (65 to 81)
< 50	3%
50 to <60	15%
≥ 60 to <70	18%
≥ 70 to <80	33%
≥ 80 to <90	18%
> 90	12%
Proteinuria (≥ +1 by dipstick)	21%
Hypertension; Diabetes	36%; 9%
HIV-associated nephropathy	3%

SD, standard deviation; IQR, interquartile range; Cr, creatinine; CrCl, creatinine clearance

Figure Legends

Figure 1:.Changes in Serum Creatinine (a) and CrCl by Baseline CrCl (b)

(a)



(b)