Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate in Asian Subjects with Human Immunodeficiency Virus 1 Infection: A Sub-Analysis of Phase 3 Clinical Trials

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The efficacy and safety of a single tablet regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) were analyzed in Phase 3 clinical trials in antiretroviral therapy (ART)-naïve and ART-experienced Asian subjects infected with human immunodeficiency virus (HIV)-1. Studies GS-US-236-102 and GS-US-236-103 were randomized, double-blind, placebo-controlled, 144-week studies conducted in ART-naïve subjects, comparing E/C/F/TDF versus efavirenz (EFV)/F/TDF or ritonavir-boosted atazanavir (ATV+RTV) plus emtricitabine/tenofovir DF (F/TDF), respectively. Studies GS-US-236-115 and GS-US-236-121 were randomized, open-label, 96-week long conducted in ART-experienced subjects, who switched to E/C/F/TDF from ritonavir-boosted protease inhibitors (PI+RTV)+F/TDF, or non-nucleoside reverse transcriptase inhibitors (NNRTI)+F/TDF regimens. The E/C/F/TDF appeared to have sustained efficacy and safety and was well tolerated in the small number of ART-naïve and ART-experienced Asian subjects.

Key Words: Human immunodeficiency virus; Antiretroviral therapy; Asian Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
The single tablet regimen (STR) containing elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate (E/C/F/TDF) is a recommended regimen in the guidelines of the US Department of Health and Human Services and the European acquired immunodeficiency syndrome (AIDS) Clinical Society [1, 2]. In two Phase 3 randomized, double-blind, placebo-controlled clinical trials in ART-naïve adults infected with the human immunodeficiency virus (HIV)-1, E/C/F/TDF (n = 701) demonstrated non-inferior efficacy at week 48, 96, and 144 compared to the STR of efavirenz (EFV)/F/TDF (GS-US-236-0102, Study 102) and the ritonavir-boosted atazanavir (ATV+RTV) plus emtricitabine/tenofovir DF (F/TDF, GS-US-236-0103, Study 103) as well as favorable safety and tolerability [3-9]. Studies GS-US-236-115 (STRATEGY-PI) and GS-US-236-121 (STRATEGY-NNRTI) examined the efficacy, safety, and tolerability of switching to E/C/F/TDF from ritonavir-boosted protease inhibitors (PI+RTV)+ F/TDF or non-nucleoside reverse transcriptase inhibitors (NNRTI)+F/TDF regimens, respectively, in virologically suppressed (HIV-1 RNA <50 copies/mL), ART-experienced adult subjects [10-13]. At week 48 and 96, the STRATEGY-PI study showed that switching to E/C/F/TDF from a PI+RTV-based regimen was associated with significantly higher rates of virological success, lower triglyceride levels, and improvements in self-reported diarrhea and bloating [14]. The STRATEGY-NNRTI study showed the non-inferior efficacy of E/C/F/TDF versus re-

Table 1. Baseline characteristics: Asian subpopulation studies

| Characteristic, % (n) | ART-naive Studies 102 and 103 | ART-experienced Studies 115 and 121 |
|-----------------------|-------------------------------|-----------------------------------|
|                       | E/C/F/TDF (n=23) | EFV/F/TDF (n=10) | ATV+RTV/F/TDF (n=17) | STRATEGY-PI (n=7) | STRATEGY-NNRTI (n=9) |
| **Median Age, years (range)** | 33 (19-48) | 32 (25-49) | 35 (19-52) | 33 (22-45) | 45 (40-51) |
| Male | 83 (19) | 90 (9) | 88 (15) | 71 (5) | 100 (4) |
| Asymptomatic HIV Infection | 87 (20) | 100 (10) | 82 (14) | 54 (4) | 100 (2) |
| **Country of Enrollment** | | | | | |
| USA | 35 (8) | 100 (10) | 18 (3) | 14 (1) | 100 (4) |
| Thailand | 30 (7) | 0 | 24 (4) | 71 (5) | 0 |
| Europe | 26 (6) | 0 | 6 (1) | 71 (5) | 0 |
| Other<sup>a</sup> | 9 (2) | 0 | 53 (9) | 14 (1) | 0 |
| **Median HIV-1 RNA, log10c/mL** | 4.8 | 4.6 | 4.6 | 4.8 | 4.6 |
| >100,000 c/mL | 35 (8) | 30 (3) | 24 (4) | 35 (8) | 30 (3) |
| Mean CD4+ T cell count, cells/mm<sup>3</sup>, (range) | 374 (220-570) | 338 (152-653) | 346 (51-507) | 548 (327-996) | 478 (385-570) |
| ≤350 | 52 (12) | 60 (6) | 47 (8) | 14 (1) | 50 (1) |
| ≤200 | 0 | 20 (2) | 12 (2) | 14 (1) | 0 |
| **Median GFR by Cockcroft Gault, mL/min** | 100 | 93 | 105 | 104 | 104 |

<sup>a</sup>Other: E/C/F/TDF; Australia (2); ATV+RTV+TVD; Australia (7); Canada (2).

<sup>b</sup>Other: E/C/F/TDF; Switzerland (1); NNRTI+TVD: Australia (1).

E, elvitegravir; C, cobicistat; F, emtricitabine; TDF, tenofovir disoproxil fumarate; EFV, efavirenz; ATV, atazanavir; RTV, ritonavir; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; GFR, glomerular filtration rate.
maintaining on the NNRTI+ F/TDF regimen, improvement in patient-reported outcomes (PROs) related to NNRTI-associated neuropsychiatric side effects, and greater treatment satisfaction scores [15]. There is limited data on the efficacy and safety of current antiretroviral therapies in Asian subjects infected with HIV-1. Here, we report a sub-analysis of E/C/F/TDF efficacy and safety data in Asian subjects enrolled in Studies 102 and 103 at week 144 as well as Studies 115 and 121 at week 96.

In the two ART-naïve studies, 1,408 subjects (E/C/F/TDF; n = 701 vs. EFV/FTC/TDF; n = 352 vs. ATV+RTV+ F/TDF; n = 355) were enrolled and received at least one dose of a study drug. In the two studies with ART-experienced, virologically suppressed subjects, 867 (Study 115: E/C/F/TDF; n = 293 vs. PI+RTV+ F/TDF; n = 140 and Study 121: E/C/F/TDF; n = 291 vs. NNRTI+ F/TDF; n=143) were enrolled and received at least one dose of a study drug. In these four clinical trials, 72 Asian subjects consisting of 50 ART-naïve (E/C/F/TDF; n=23; EFV/ FTC/TDF; n = 10; and ATV+RTV+ F/TDF; n = 17) and 22 ART-experienced, virologically suppressed (Study 115: E/C/F/TDF; n = 7 and PI+RTV+ F/TDF; n=2; and Study 121: E/C/F/TDF and n = 4; NNRTI+ F/TDF; n=9) were included in this sub-analysis of the E/C/F/TDF data [16].

The baseline demographics and disease characteristics of the ART-naïve (Studies 102 and 103, pooled) and ART-experienced (Study 115 and Study 121, separately) subjects on E/C/F/TDF were as follows: median age 33, 33, and 45 years; male: 83%, 71%, and 100%; mean CD4 count: 374, 548, and 402 cells/mm$^3$; and median estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault method: 100, 104, and 125 mL/min, respectively (Table 1).

Similar high rates of virological success (HIV-RNA <50 copies/mL, FDA Snapshot Analysis) and comparable immunological outcomes were observed in the ART-naïve and ART-experienced subjects on E/C/F/TDF. In the ART-naïve subjects, the virological success (HIV-1 RNA <50 copies/mL) was 91, 80, and 76% with E/C/F/TDF, EFV/F/TDF, ATV+RTV+ F/TDF, respectively at week 144. The mean CD4+ T cell count (/mm$^3$) increased from baseline through week 144 (235, E/C/F/TDF; 161, EFV/F/TDF; and 250, ATV+RTV+ F/TDF). In the ART-experienced, virologically suppressed subjects, the virological success (maintenance of HIV-1 RNA <50 copies/mL) of the E/C/F/TDF regimen was 86 and 100% (Studies 115 and 121, respectively) at week 96. The virological success rates for subjects who remained on the PI+RTV+ F/TDF or NNRTI+ F/TDF regimens were 100 and 67%, respectively, both at week 96. The mean CD4+ T cell count increases were similar for E/C/F/TDF in both Studies 115 and 121: 61 and 71 cells/mm$^3$ compared to -30 and 162 cells/mm$^3$ for patients who remained on the PI+RTV+ F/TDF and NNRTI+ F/TDF regimens, respectively (Fig. 1).

The overall safety and tolerability of E/C/F/TDF in both ART-naïve and ART-experienced subjects were similar to that of E/C/F/TDF in the overall populations enrolled in the four studies. In the ART naïve subjects, the most common study drug-related adverse events (AEs) with E/C/F/TDF were nausea (n = 4 vs. EFV/F/TDF, n = 0 and ATV+RTV+ F/TDF, n = 5), abnormal dreams (n = 2 vs. 5 and 1, respectively), diarrhea (n = 2 vs. 0 and 3, respectively) and dizziness (n = 1 vs. 2 and 2, respectively). Grade 3AEs occurred in subjects with similar frequency between E/C/F/TDF (17%, n = 4) and EFV/F/TDF (20%, n = 2) while no subjects in the ATV+RTV+ F/TDF treatment arm experienced this Grade. Furthermore, there were no Grade 4 AEs. There were few study drug discontinuations due to AEs in the ART-naïve subjects and the frequency was similar between the treatment arms |E/C/F/TDF; n = 1 due to
lymphoma; EFV/F/TDF, n=1 due to presyncope; and AT-
V+RTV+F/TDF, n = 2 due to gastrointestinal disorder consist-
ing of diarrhea (one subject) and nausea, vomiting, and flatu-
ence (one subject, who also had dizziness)]. In the ART-experienced subjects, the most common study drug-re-
lated AEs with E/C/F/TDF in Study 115 were, enlarged parotid
and alopecia (n = 1 each) and in Study 121, increased
weight (n = 1) and GFR (n = 1 in male, 47 years old, observed
as Grade 1). Only one Grade 3-4 AE occurred in the ART-ex-
perienced subjects, which was a subject with a clavicle frac-
ture treated on E/C/F/TDF. There were no subjects on E/C/F/
TDF in the ART-experienced studies that discontinued the
study drug because of AEs and no subjects in either the ART-
naïve or ART-experienced discontinued E/C/F/TDF because
of renal AEs. The treatment emergent Grade 3-4 laboratory
abnormalities observed with E/C/F/TDF were all Grade 3 (al-
anine transaminase [ALT], n = 2; aspartate transaminase
[AST], n = 1; and hyperuricemia, n = 1) in ART-experienced
subjects.

Cobicistat induced a slight increase in serum creatinine
(SCr) with a consequent reduction in the eGFR in Phase 1 and
2 clinical trials [17-19]. The changes in SCr are caused by the
inhibition of tubular creatinine secretion with no effect on the
actual glomerular filtration rate, as measured by the clearance
of iohexol [18]. In this sub-analysis in Asian subjects, the me-
dian changes from baseline in SCr were similar to that ob-
erved in the overall study population on E/C/F/TDF. The me-
dian change from baseline in the SCr of the ART-naïve
subjects was 0.14 mg/dL with E/C/F/TDF vs. -0.03 mg/dL
with EFV/F/TDF and 0.04 mg/dL with ATV+RTV+F/TDF. Fur-
thermore, the values for the ART-experienced subjects were
0.06 mg/dL with E/C/F/TDF vs. -0.18 mg/dL with PI+RTV+F/
TDF (Study 115) and 0.05 mg/dL with both E/C/F/TDF and
NNRTI+F/TDF (Study 121).

In Asian subjects, the median changes from baseline in the
fasting lipid parameters [total cholesterol (TC) and high-den-
sity lipoprotein (HDL)] were slight with E/C/F/TDF, which re-
sulted in minimal median changes in the TC:HDL ratio [ART-
naïve (0.1) and ART-experienced (Studies 115 and 121, 0.2
and 0.0, respectively)] (Fig. 2)

A limitation of this sub-analysis is the small number of Asian
subjects, who accounted for 4 and 3% of the overall popula-
tion of the participants enrolled in the ART-naïve and ART-
experienced studies. This restricted the definitive assessment of
the safety and tolerability of E/C/F/TDF in Asian subjects, and
may limit generalization of the results.

In these sub-studies of Phase 3 clinical trials of E/C/F/TDF,
in Asian subjects on E/C/F/TDF resulted in minimal changes in the TC:HDL ratio and were similar to those in the overall study population. In summary, from this sub-analysis in a small number of Asian subjects, E/C/F/TDF appears to have sustained efficacy and is safe and well-tolerated based on the available data in both the ART-naïve and ART-experienced Asian subjects.

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Conflicts of Interest

No conflicts of interest.

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