

Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection

Calvin Cohen, Richard Elion, Peter Ruane, David Shamblaw, Edwin DeJesus, Bruce Rashbaum, Steven L. Chuck, Kitty Yale, Hui C. Liu, David R. Warren, Srinivasan Ramanathan and Brian P. Kearney

Objective: To assess the safety and efficacy of two, single-tablet regimens for the initial treatment of HIV infection.

Design: Phase 2, randomized, double-blind, double-dummy, multicenter, active-controlled study.

Methods: Antiretroviral treatment-naïve adults with a screening HIV-1 RNA at least 5000 copies/ml and a CD4 cell count more than 50 cells/ μ l were randomized 2:1 to receive fixed-dose combination tablets of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; $N=48$) or efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF; $n=23$) for 48 weeks. The primary endpoint was proportion of participants with HIV-1 RNA less than 50 copies/ml at week 24.

Results: Participants receiving EVG/COBI/FTC/TDF exhibited a more rapid decline in HIV-1 RNA and a greater proportion suppressed viral load to less than 50 copies/ml than participants receiving EFV/FTC/TDF. Both EVG/COBI/FTC/TDF and EFV/FTC/TDF resulted in high rates of viral suppression and increases in CD4 cell count. Ninety and 83% of participants suppressed HIV-1 RNA to less than 50 copies/ml both at the 24-week and 48-week visits for EVG/COBI/FTC/TDF and EFV/FTC/TDF, respectively. Once-daily administration of EVG/COBI/FTC/TDF provided a mean EVG trough concentration 10-fold over its protein binding-adjusted IC_{95} across study visits. EVG/FTC/TDF/GS-9350 was generally well tolerated with a lower rate of drug-related central nervous system (17%) and psychiatric (10%) adverse events versus EFV/FTC/TDF (26 and 44%, respectively). Decreases in estimated glomerular filtration rate occurred within the first few weeks of dosing in participants receiving EVG/COBI/FTC/TDF, remained within the normal range and did not progress at week 24 or 48; no participant experienced a clinical adverse event or discontinued study drug due to changes in serum creatinine or renal function.

Gilead Sciences Inc., Foster City, California, USA.

Correspondence to Brian P. Kearney, Gilead Sciences Inc., 333 Lakeside Drive, Foster City, CA 94404, USA.

Tel: +1 650 522 3000; e-mail: bkearney@gilead.com

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Conclusion: Once-daily EVG/COBI/FTC/TDF achieved and maintained a high rate of virologic suppression with fewer central nervous system and psychiatric adverse events compared to a current standard-of-care regimen of EFV/FTC/TDF.

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Introduction

Historically, international treatment guidelines recommend initial therapy for treatment-naive, HIV-infected patients be composed of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI) – usually efavirenz (EFV) – or a ritonavir-boosted protease inhibitor (PI/r) [1–3]. Recently, an integrase inhibitor-based regimen was added as a preferred regimen by some guidelines [1,2]. Although current regimens have been successful in reducing the morbidity/mortality associated with HIV disease, most require multiple pills, have side-effects and often, require twice-daily dosing. Dosing frequency and pill burden remain key obstacles to patients maintaining long-term adherence needed to avoid treatment failure and subsequent use of more inconvenient, less well tolerated and ultimately more expensive regimens [4–9]. There remains a need for new antiretroviral agents with improved safety profiles and simplified, once-daily single-tablet regimens (STRs) for the treatment of HIV infection.

Elvitegravir (EVG) is an HIV-1 strand-transfer integrase inhibitor with potent in-vitro and in-vivo activity [10,11]. EVG is metabolized via cytochrome P450 (CYP) 3A4; thus, co-administration with potent CYP3A inhibitors such as ritonavir or the investigational pharmacoenhancer cobicistat (GS-9350, COBI) substantially increases ('boost') its systemic exposure, including providing high trough (C_{min}) concentrations and allowing for once-daily dosing [12–14]. EVG has been generally well tolerated in clinical studies and at this time is under phase 3 evaluation in treatment-naive and treatment-experienced patients [15].

Liabilities of low-dose ritonavir include adverse events and intolerance by some patients, physicochemical properties that limit coformulation potential with other antiretrovirals and the need for an additional prescription for patients [16]. COBI is devoid of anti-HIV activity with less negative effects on adipocyte function *in vitro* and can be coformulated with other agents requiring boosting, including EVG and protease inhibitors [17].

The co-formulation of EVG with COBI and the standard-of-care NRTI backbone emtricitabine/tenofo-

vir disoproxil fumarate (FTC/TDF) into a STR has been described previously [17,18]. We now report the results of a 48-week, randomized, double-blind, multicenter, active-controlled study of two once-daily STRs: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; 'Quad') versus efavirenz/emtricitabine/tenofovir DF (EFV/FTC/TDF, Atripla) in HIV-1-infected, antiretroviral treatment-naive adult participants [19,20].

Methods

Study design

Key entry criteria were adults (≥ 18 years) with a screening plasma HIV-1 RNA of at least 5000 copies/ml and a CD4 cell count more than 50 cells/ μ l, no prior use of any approved or experimental anti-HIV drug and no NRTI, NNRTI or primary protease inhibitor genotypic resistance mutations [by International AIDS Society (IAS)-USA guidelines], normal ECG, estimated creatinine clearance (glomerular filtration rate, eGFR; Cockcroft-Gault) at least 80 ml/min, aspartate aminotransferase/alanine aminotransferase (AST/ALT) 2.5 times or less the upper limit of normal (ULN) and total bilirubin 1.5 mg/dl or less and a negative serum pregnancy test (as applicable). Participants were excluded if they were hepatitis B or C-coinfected, exhibited a new AIDS-defining condition within 30 days of screening or vaccination within 90 days of study drug dosing. The study was conducted in the United States from March 2009 (screening opening and closing) through March 2010 (48-week visits) under Good Clinical Practice and Institutional Review Boards' review. Prior to study screening, all participants signed written informed consent. This study was posted on clinicaltrials.gov (NCT00869557).

Eligible participants were randomized centrally by a third party interactive voice/web response system, stratified by screening HIV-1 RNA level (\leq or $> 100\,000$ copies/ml) in a 2:1 manner (block size of 6) to treatment with either EVG/COBI/FTC/TDF administered once-daily with food ($n = 50$) or EFV/FTC/TDF at bedtime ($n = 25$); participants received placebo tablets matching the alternate treatment. All parties involved in the study

(patients, care providers and site, CRO and Sponsor staff) were blinded to treatment.

Study visits occurred at screening, baseline and weeks 2, 4, 8, 12, 16, and then every 8 weeks through week 48. Laboratory analyses (hematology, serum chemistries and urinalysis; Covance Laboratories, Indianapolis, Indiana, USA), HIV-1 RNA (AMPLICOR HIV-1 Monitor assays; Roche Molecular Systems, Pleasanton, California, USA) and physical examinations were performed at all study visits. HIV-1 genotype (reverse transcriptase and protease) was analyzed at screening (Covance Laboratories). Reverse transcriptase and protease (PhenoSense GT Assay) and integrase inhibitor (PhenoSense Integrase Assay, Monogram Biosciences, South San Francisco, California, USA) resistance testing was performed on participants with HIV-1 RNA more than 400 copies/ml at week 24 or 48 or upon early discontinuation of study drugs. Single time-point blood draws were collected in all participants/visits with targeted trough samples (collected 20–25 h post-EVG/COBI/FTC/TDF dose) obtained at weeks 8, 24 and 48; a pharmacokinetic substudy was conducted at week 2.

Statistical methods

The primary analysis objective was the efficacy of EVG/COBI/FTC/TDF versus EFV/FTC/TDF as determined by viral suppression defined as HIV-1 RNA less than 50 copies/ml at week 24. Secondary objectives were the safety and tolerability of the regimens and viral suppression through week 48. Primary efficacy analyses were intent-to-treat, missing equals failure (ITT, M = F). This study was not powered for efficacy comparisons between treatments; however, an *a priori* planned analysis included the point estimate of treatment difference and the associated two-sided 95% confidence interval (CI) in the response rates, stratified by baseline HIV-1 RNA. All patients who took at least one dose of study drugs were included in the analysis of safety and tolerability that included adverse events and laboratory abnormalities occurring within 30 days of study drug discontinuation.

Results

Seventy-one participants were randomized and received study drugs. Baseline demographics and disease characteristics were similar ($P > 0.1$) between the two treatment groups. Ninety-two (92) percent of participants were men, mean (SD) age was 36 (9.1) years, 24% of participants were black, 72% were white and approximately 10% self-identified as Hispanic. Mean (SD) weight and BMI were 82 (13) kg and 26.5 (3.9) kg/m², respectively. Mean HIV-1 RNA level at baseline was 4.59 log₁₀ copies/ml; the median CD4 cell count was 394 cells/μl. Sixty-five (92%) participants were on

blinded study drug through week 24 and remained so through week 48.

Treatment with EVG/COBI/FTC/TDF was associated with more rapid achievement of HIV-1 RNA less than 50 copies/ml than EFV/FTC/TDF ($P < 0.05$ at weeks 2, 4 and 8; Fig. 1). The proportions of participants with plasma HIV-1 RNA less than 50 copies/ml at week 24 were 90% (43/48) in the EVG/COBI/FTC/TDF group and 83% (19/23) in the EFV/FTC/TDF group (ITT M = F). At week 48, response rates for HIV-1 RNA were identical to those at week 24 for both treatment arms, with 90 and 83% of participants with viral suppression to less than 50 copies/ml. The stratum-weighted difference (95% CI) in response rates between the two treatment groups (EVG/COBI/FTC/TDF – EFV/FTC/TDF) was +5.0% (–11 to +21.1%) at week 24 and +8.4% (–8.8 to +25.6%) at week 48. Greater than 95% of participants on study drugs (ITT Missing = Excluded) in both treatment arms were suppressed to less than 50 copies/ml at both weeks 24 and 48. All unsuppressed participants at week 48 ($n = 3$) were suppressed to less than 50 copies/ml at their subsequent study visit. One of these participant experienced confirmed virologic rebound in HIV-1 RNA at the week 48 visit secondary to documented noncompliance to study drugs based on return of unused study medication at study visits. This participant was receiving and continued treatment on study with EFV/FTC/TDF and re-suppressed HIV-1 RNA to less than 50 copies/ml at the next study visit.

In participants receiving EVG/COBI/FTC/TDF, greater than 90% of EVG trough concentrations (C_{\min}) across all visits were above the protein binding-adjusted IC₉₅ with a mean C_{\min} to protein-binding adjusted IC₉₅ ratio ('IQ₉₅') of 10-fold. Results were similar in participants participating in the intensive pharmacokinetic substudy at week 2 (mean IQ₉₅: 9.4, $n = 12$) and all participants in the study

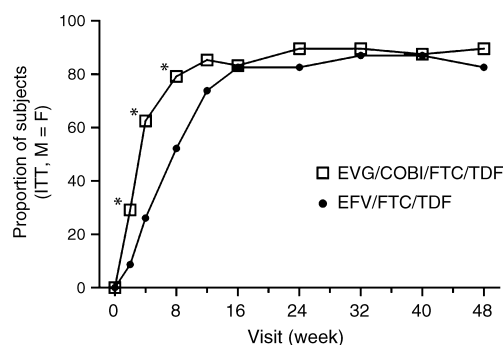


Fig. 1. Proportion of participants with HIV-1 RNA less than 50 copies/ml by visit. *Significant difference in proportion of participants less than 50 copies/ml, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) versus efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF; $P < 0.05$, Cochran–Mantel–Haenszel test).

at trough concentrations measured at weeks 8, 24 and 48 (mean IQ_{95} values: 7.3, 9.3 and 8.8; $n = 38$ to 44 by visit). Ten participants accounted for the 20 (10%) samples below the IC_{95} for EVG ($n = 1-5$ samples/participant). In these participants, individual EVG concentrations were either more than three-fold ($n = 4$ participants) above the protein binding-adjusted IC_{50} or below the limit of quantitation (BLQ, 20 ng/ml; $n = 6$ participants).

Treatment with EVG/COBI/FTC/TDF resulted in a median increase in CD4 cell count of 123 and 205 cells/ μ l baseline to week 24 and 48, respectively versus 124 and 139 cells/ μ l for the EFV/FTC/TDF group.

Six participants, three in each arm, discontinued study drug prematurely, all within the first 24 weeks. One participant receiving EFV/FTC/TDF discontinued study drug due to an adverse event (suicidal ideation) that was assessed as moderate in severity and related to study drug. No participant receiving EVG/COBI/FTC/TDF discontinued for an adverse event. Three participants were lost to follow-up, one withdrew consent and the final participant was discontinued by the investigator due to failure to return for study visits.

Through 48 weeks, the majority of treatment-emergent adverse events were assessed as mild or moderate in severity. No deaths or pregnancies occurred. Three participants experienced serious adverse events (SAEs), two receiving EVG/COBI/FTC/TDF (cellulitis of male external genital organ and pneumonia) and one on EFV/FTC/TDF (vaccination site reaction and B-cell lymphoma, leucopenia and thrombocytopenia). No severe (grade 3) or life-threatening (grade 4) or SAEs were judged by the investigator to be related to study treatments. Two participants in each arm experienced grade 3 and/or life-threatening (grade 4) treatment-emergent adverse events. In participants receiving EFV/FTC/TDF, one had grade 3 lymphadenopathy and B-cell lymphoma and grade 4 leucopenia and thrombocytopenia (also an SAE); a second participant had grade 3 neutropenia. One participant receiving EVG/COBI/FTC/TDF experienced grade 3 (and SAE) pneumonia; a second reported grade 3 exacerbation of anal warts. Study drug-related nervous system adverse events, including headache, somnolence, dizziness, disturbance in attention, lethargy and mental impairment were more common in participants receiving EFV/FTC/TDF (26%) than EVG/COBI/FTC/TDF (10%, $P = 0.16$, Fisher's exact test). Study drug-related grade 1-4 psychiatric disorders (abnormal dreams, insomnia, nightmare, affect lability, anxiety, anxiety disorder, depression, euphoric mood, hallucination, major depression, mood swings, suicidal ideation and terminal insomnia) were reported in more participants receiving EFV/FTC/TDF (43%) than EVG/COBI/FTC/TDF (17%, $P = 0.02$, Fisher's exact test). These adverse events occurred more frequently, but not exclusively, in the first 24 weeks of

treatment. Study drug-related treatment-emergent adverse events that occurred in more than two participants receiving EVG/COBI/FTC/TDF were diarrhea ($n = 4$), nausea (3), fatigue (4) and abnormal dreams (4).

The majority of treatment-emergent laboratory abnormalities were grade 1 or 2 in severity. There were no confirmed grade 3/4 treatment-emergent laboratory abnormalities in participants receiving EVG/COBI/FTC/TDF; a single participant receiving EFV/FTC/TDF experienced confirmed, decreased neutrophil counts that resolved during ongoing administration of blinded study drug. Small changes from baseline to week 48 were observed in both treatment arms in fasting serum cholesterol (total, low and high-density lipoprotein) and triglycerides. Mean \pm SD increases in total and LDL cholesterol were 20 ± 25 and 12 ± 20 mg/dl, respectively, in participants receiving EVG/COBI/FTC/TDF and 30 ± 33 and 22 ± 33 mg/dl for those receiving EFV/FTC/TDF. Mean \pm SD changes in triglycerides were 31 ± 102 and 20 ± 60 mg/dl for EVG/COBI/FTC/TDF and EFV/FTC/TDF, respectively. Decreases in eGFR within the normal range occurred within the first 2 weeks of dosing and stabilized without evidence of progression at weeks 24 and 48 (Table 1). In both treatment groups, the mean eGFR at baseline was 131 ml/min; at week 48, the mean \pm SD values were 109 ± 26.1 ml/min in the EVG/COBI/FTC/TDF group and 127 ± 45.6 ml/min in participants receiving EFV/FTC/TDF. A single participant, receiving EVG/COBI/FTC/TDF experienced a confirmed grade 1 laboratory abnormality of elevated serum creatinine; no participants experienced hypophosphatemia. No participants discontinued study drug due to changes in serum creatinine or eGFR. No notable changes in vital signs or physical examination were observed in this study.

Discussion

This phase 2 study represents the first evaluation of an HIV-1 integrase inhibitor-based STR for the initial treatment of HIV-1 infection. This study also represents the first randomized, blinded study of the STR of EFV/FTC/TDF.

Both EVG/COBI/FTC/TDF and EFV/FTC/TDF demonstrated high rates of viral suppression and increases in CD4 cell count over 24 and 48 weeks of treatment in HIV-1-infected, antiretroviral treatment-naïve participants. Participants receiving EVG/COBI/FTC/TDF rapidly achieved undetectable levels of HIV-1 RNA with 90 and 96% suppressed by the strict, intent-to-treat, missing = failure analysis and 'as-treated' (ITT, $M = E$), respectively. The rapidity of viral suppression and robust antiviral response observed with EVG/COBI/FTC/TDF in this study is consistent with the potency of

Table 1. Baseline characteristics, efficacy and safety results.

	EVG/COBI/FTC/TDF (n = 48)		EFV/FTC/TDF (n = 23)	
Baseline characteristics				
Mean age (years)	36		35	
Male sex (%)	92		91	
Race (black/white, %)	25/69		22/78	
Mean Log ₁₀ HIV-1 RNA (copies/ml)	4.59		4.58	
Median CD4 cell count (cells/ml)	354		436	
Efficacy				
	Week 24	Week 48	Week 24	Week 48
Proportion with HIV RNA <50 copies/ml (ITT, M=F)	90%	83%	90%	83%
Proportion with HIV RNA <50 copies/ml (ITT, M=E)	96%	95%	96%	95%
Median increase in CD4 cells/ μ l	123	205	124	139
Safety				
	Through week 48			
Drug-related, treatment-emergent AEs (n, %) ^a	22 (46%)		13 (57%)	
Nervous system disorders ^b	5 (10%)		6 (26%)	
Psychiatric disorders ^c	8 (17%)		10 (43%)	
Gastrointestinal disorders ^d	8 (17%)		3 (13%)	
Mean change from baseline in eGFR ^e : ml/min (% Δ)				
Week 2	-13.1 (-9%)		-1.1 (-1%)	
Week 24	-18.0 (-13%)		-6.6 (-5%)	
Week 48	-19.7 (-14%)		-5.5 (-4%)	

AE, adverse event; eGFR, estimated glomerular filtration rate.

^aGrade 1 through 4.

^bHeadache, somnolence, dizziness, disturbance in attention, lethargy, mental impairment [elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) versus efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF), $P=0.16$, Fisher's exact test].

^cAbnormal dreams, insomnia, nightmare, affect lability, anxiety, anxiety disorder, depression, euphoric mood, hallucination, major depression, mood swings, suicidal ideation, terminal insomnia (EVG/COBI/FTC/TDF versus EFV/FTC/TDF, $P=0.02$, Fisher's exact test).

^dDiarrhea, nausea, flatulence, defecation urgency, dyspepsia, vomiting.

^eEstimated glomerular filtration rate or estimated creatinine clearance by Cockcroft–Gault equation.

HIV integrase inhibitors and robust COBI-boosted EVG exposures in virtually all participants and visits [21,22]. No participants experienced virologic failure with this once-daily STR.

Safety data demonstrated that EVG/COBI/FTC/TDF tablets, dosed daily for up to 48 weeks, were generally well tolerated with no discontinuations due to adverse events or laboratory toxicities. Fewer participants receiving EVG/COBI/FTC/TDF experienced nervous system or psychiatric symptoms that are commonly reported by patients receiving a regimen that includes EFV [23–30]. Decreases in eGFR occurred within the first few weeks of dosing in participants receiving EVG/COBI/FTC/TDF which did not progress at either week 24 or 48. A pharmacokinetic/pharmacodynamic study has shown that administration of COBI results in small increases in serum creatinine but does not affect actual glomerular filtration rate when measured with a probe drug iohexol (data on file; Gilead Sciences Inc., Foster City, California, USA). These data indicate the observed increase in serum creatinine is due to an effect on the tubular secretion of serum creatinine.

High rates of efficacy and a favorable safety profile are required for any treatment regimen in the modern era. EFV is associated with central nervous system and psychiatric side-effects and hyperlipidemia; it may cause fetal harm when administered during the first trimester (pregnancy category D), thus limiting its use in women of

childbearing potential. Some patients experience poor gastrointestinal tolerability and/or hyperlipidemia and are required to take three to four pills per day with boosted protease inhibitor-based regimes [16]. These phase 2 results support the ongoing evaluation of this once-daily STR of EVG/COBI/FTC/TDF as a potential attractive alternative for treatment-naïve patients relative to currently available therapies, including the only currently available STR EFV/FTC/TDF.

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