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Bioequivalence of Two Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate 600/200/300 mg Fixed-Dose Combination Tablets in Healthy Thai Male Volunteers under Fasting Conditions

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Abstract

Fixed-dose combination tablet formulation of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg is an antiretroviral therapy comprising one non-nucleoside reverse-transcriptase inhibitor and two nucleoside reverse-transcriptase inhibitors to control human immunodeficiency virus infection. A generic fixed-dose combination product, GPO-VIR T® had been developed to enhance patient adherence and reduce cost of lifelong treatment. A comparative randomized, single dose, two-way crossover, open-label bioequivalence study was conducted in 52 healthy Thai male volunteers. A single dose of the test (GPO-VIR T®) or reference (Atripla®) formulation was given in each period under fasting conditions. The washout duration between two treatments was 28 days. Blood samples were collected at predefined sampling time points up to 72 hours after oral administration. Plasma concentrations of efavirenz, emtricitabine and tenofovir, an active metabolite of tenofovir disoproxil fumarate were simultaneously determined using a validated liquid chromatography tandem mass spectrometry. The pharmacokinetic parameters were computed for each drug in each formulation using non-compartmental model. Two one-sided tests for bioequivalence were performed and showed no significant difference between the test and reference formulations for all three analytes. The 90% confidence intervals for the geometric least square mean ratio of log-transformed AUC_{0-72}, $AUC_{0-\infty}$ and C_{max} for each analyte between the test and reference formulations were calculated and they fell within the acceptance range of 80.00-125.00%. Both products were well tolerated. Adverse events found in this study were mild and could recover without any medical treatment. In conclusion, two formulations, GPO-VIR T® and Atripla® were bioequivalent and can be used interchangeably as the same efficacy and tolerability can be anticipated.

Keywords: Efavirenz; Emtricitabine; Tenofovir; Fixed-Dose; Bioequivalence; Pharmacokinetics

Introduction

Human immunodeficiency virus (HIV) is a virus that attacks the CD4+ T cells leading to immune dysregulation and complications, especially opportunistic infections [1]. Currently, HIV cannot be cured but many antiretroviral therapies (ARTs) are used to suppress viral replication aiming to reduce a viral load to undetectable level. Infected patients must continue the ART agents throughout their lives. WHO guideline recommended the ART regimen for naïve adult patients combining one non-nucleoside reverse-transcriptase inhibitor (NNRTI) and two nucleoside reverse-transcriptase inhibitors (NRTIs) to prevent the drug resistance [2]. High adherence to the therapy is important for achieving desirable therapeutic outcomes. Therefore, the fixed-dose combination regimen is developed to enhance patient adherence and to reduce the risk of drug resistance by allowing patients to take three antiviral agents altogether in a single tablet.

Efavirenz (EFV) is an NNRTI agent in the formulation, which is more preferred than nevirapine due to less toxicity and greater efficacy [3]. A peak serum concentration of EFV is achieved within 5 hours after oral administration. Food significantly increases the bioavailability of EFV leading to higher risk of toxicity [3]. For this reason, combination formulation containing EFV should be administered on an empty stomach [4]. EFV is primarily metabolized by CYP2B6 and CYP3A4 enzymes and about 16-61% of EFV is eliminated unchanged in feces [3,5,6]. It has a long half-life around 52-76 hours after single oral dosing versus 40-55 hours after multiple dosing owing to auto-CYP enzyme induction [5,6].

Two NRTIs in the formulation are emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). FTC is a cytosine analogue whereas TDF is a prodrug of adenosine analogue rapidly hydrolyzed in the blood to active metabolite, tenofovir (TFV). The maximum serum concentrations of FTC and TFV are attained within 1-2 hours after oral administration [5]. Both FTC and TFV are renally metabolized and excreted as unchanged form in the urine accounted for more than 70% of the administered dose. Therefore, dose adjustment is required in patients with renal insufficiency. Elimination half-life of FTC and TFV are approximately 10 and 17 hours, respectively which are shorter than EFV [3,5].

EFV/FTC/TDF combination formulation in the standard daily dosage of 600 mg for EFV, 200 mg for FTC and 300 mg for TDF represents the 'one pill day' concept [3,5,7]. The fixed-dose combination formulation is available as registered trademark Atripla®, Gilead Sciences, Inc., USA [4]. However, the branded product may be expensive for prolonged and continuous use in some patients, thereby developing resistance to ARTs. The Government Pharmaceutical Organization (GPO), Thailand had developed the generic fixed-dose combination product, GPO-VIR T® at a reduced cost to serve as an alternative product for physicians and patients. To ensure that the generic product maintained the same quality and tolerability as the reference product, the bioequivalence study was conducted. The results from this study illustrated the rate and extent of absorption of drugs in the test (GPO-VIR T®) and reference formulations (Atripla®). The adverse events reported in this study were used to evaluate tolerability of both formulations in Thai population.

Materials and Methods

Study Products

GPO-VIR T® 600/200/300 mg of EFV/FTC/TDF (Lot No. S580201) manufactured by GPO was used as the test product and Atripla® (Lot No. SWPYM) of Gilead Sciences, Inc., USA was used as the reference product.

In Vitro Dissolution Profile Test

Twelve tablets of each test and reference product were used for evaluation of dissolution. The tests were performed using USP dissolution apparatus II with 100 rpm agitation speed. The dissolution rate and solubility were characterized in 1000 mL of 4 different dissolution media with addition of 2% of sodium lauryl sulfate (SLS) including water, 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8. Ten mL of each sample was collected at 10, 15, 20, 30 and 45 minutes. The samples were analyzed using high-performance liquid chromatography couple with ultraviolet-visible spectrometer (UltiMate 3000, Thermo Fisher Scientific Inc., USA). The results were presented in similarity factor (f_2) which should be within the acceptance range of 50-100.

Study Subjects

The sample size was determined by considering the assumptions based on the T/R ratio 95%, the possible maximum intra-subject variability about 25% [8], significance level 5%, power ≥ 90% and bioequivalence limits of 80.00-125.00%. Based on the calculation, the sample size of 37 subjects would be sufficient to establish bioequivalence. However, total of 52 healthy Thai male volunteers were enrolled in the study accounted for 30% dropout and withdrawal rate. All subjects at the age between 18-55 years with a body mass index between 18-25 kg/m^2 were estimated to be healthy by assessment of medical history, physical and laboratory examinations such as complete blood count, hematocrit, hemoglobin, fasting blood sugar, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein albumin, hepatitis B antigen, anti-HIV, urine analysis and ECG.

The exclusion criteria included a history of hypersensitivity to EFV, FTC, TDF or any of the excipients, a history or presence of any diseases, clinically significant illness within 4 weeks before start the study, alcohol dependence or drug abuse, cigarette smoking, consumption of xanthine containing products or any grapefruit, pomelo, orange or orange-based products within 48 hours prior to dosing. In addition, subjects who participated in any other clinical trial or donated blood within 90 days prior to the start of study were excluded. The written informed consent was given by the study subjects before the study participation at International Bio Service Co., Ltd., Golden Jubilee Medical Center, Mahidol University, Thailand.

Study Design

The bioequivalence study was designed as a comparative randomized, single dose, two-way crossover, open-label study. The study protocol was reviewed and approved by Institute for the Development of Human Research Protections (IHRP), Department of Medical Sciences, Ministry of Public Health, Thailand. After an overnight fasting, subjects received a single oral dose of either the test or reference formulation as per the randomization schedule. Then, they switched over to the other formulation after 28-day washout period to complete crossover design. Adverse events were monitored throughout the study based on direct questioning, clinical examination, and laboratory examination. Twenty-six blood samples were collected from each subject in each study period at 0 (pre-dose), 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 24, 36, 48 and 72 hours post dose. Blood samples in vacutainers containing dipotassium ethylenediaminetetraacetate (K_2EDTA) were then centrifuged at 3,000 ± 100 rcf for 5 minutes at 10°C to separate plasma. The plasma samples were stored in two separated aliquots in freezer maintained at -55°C or colder until analysis.

Study Sample Analysis

The plasma concentrations of EFV, FTC and TFV were simultaneously measured using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS). Efavirenz-d5, Emtricitabine-[$^{2}H_{3}$-^{15}N] and Tenofovir-d7 were used as the internal standards (ISTDs) for EFV, FTC and TFV, respectively. The analytes and internal standards were extracted from plasma using solid phase extraction method. Briefly, the Oasis MCX 30 mg/1 cc cartridges were conditioned using methanol, followed by water. The samples were loaded into the conditioned cartridges. Then the cartridges were washed with 0.1 N hydrochloric acid and dried under full pressure. The analytes and internal standards were eluted from the cartridges using 5% v/v of ammonia in methanol. The eluents were evaporated at 40°C under vacuum to dryness. The residuals were reconstituted with methanol : 1 mM ammonium acetate buffer (pH 2.1) (80:20, v/v). The samples were subsequently injected into LC-MS/MS system at 10 µL.

The chromatographic separation was performed on ACE 5 CN analytical column (150×4.6 mm) which was maintained at 40°C. A gradient mobile phase system consisting of 1 mM ammonium acetate buffer (pH 2.1) and methanol was pumped into Nexera™ LC system (Shimadzu Corporation, Japan) at a flow rate of 1.5 mL/minute. The detection was done using MS/MS detector (TSQ Quantum Ultra equipped with electrospray ion source, Thermo Fisher Scientific Inc., USA) in the multiple reaction monitoring (MRM) transition of m/z 316.02 to 168.07 for EFV, m/z 248.05 to 113.11 for FTC, m/z 288.09 to 176.21 for TFV, m/z 321.10 to 173.15 for ISTD-EFV, m/z 252.06 to 132.15 for ISTD-FTC and m/z 295.13 to 183.25 for ISTD-TFV. Data analysis was performed using Xcalibur™ 3.0.63.3 and LCquan™ 2.9.0.34 (Thermo Fisher Scientific Inc., USA).

Pharmacokinetic and Statistical Analysis

Plasma concentrations of three analytes were analyzed as a function of time. The pharmacokinetic parameters were computed for each analyte in each formulation using non-compartmental model of Phoenix WinNonlin software version 6.3 (Pharsight Corporation, USA). Area under the plasma concentration-time curve from time zero to last sampling time point (AUC_{0-72}), area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), and peak concentration (C_{max}) were considered as the primary parameters. Time to peak concentration (t_{max}), elimination rate constant (λ_z) and half-life ($t_{1/2}$) were considered as the secondary parameters.

The statistical analysis was conducted using PROC GLM of SAS® version 9.3 (SAS Institute Inc., USA). The log-transformed AUC_{0-72}, $AUC_{0-\infty}$ and C_{max} were subject to analysis of variance (ANOVA). The ANOVA model included Sequence, Formulation and Period as fixed effects and Subject (Sequence) as a random effect. Sequence effect was tested using Subject (Sequence) as an error term. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level alpha = 0.05. Two one-sided tests for bioequivalence were performed by computing the 90% confidence intervals (CIs) for the geometric least squares mean ratios (test/reference) of log-transformed AUC_{0-72}, $AUC_{0-\infty}$ and C_{max}. The t_{max} values were compared using nonparametric approach, Wilcoxon signed-rank test at p = 0.05.

Results

In Vitro Dissolution Profile Test

The similarity factors (f_2) for the dissolution profiles of EFV, FTC and TDF in 4 different dissolution media are summarized in Table 1. The f_2 cannot be calculated for the dissolution of EFV determined in water + 2% SLS since the percent relative deviation of the second to the last time point was more than 10%. The dissolution profiles of test and reference products in phosphate buffer pH 6.8 + 2% SLS were accepted as similar for EFV with an f_2 value of 57. However, the f_2 of EFV dissolution profiles in 0.1 N HCl + 2% SLS and acetate buffer pH 4.5 + 2% SLS were not within the acceptance range of 50-100. The comparative dissolution profiles of FTC and TDF in all tested dissolution media were estimated to be similar owing to the accepted f_2.

Dissolution mediums	Similarity factor (f_2)		
	EFV	FTC	TDF
Water + 2% SLS	Cannot be calculated*	67	82
0.1 N HCl + 2% SLS	46	88	50
Acetate buffer pH 4.5 + 2% SLS	45	64	81
Phosphate buffer pH 6.8 + 2% SLS	57	81	89

*The percent relative deviation of the second to the last time point was more than 10%.

Table 1: The similarity factors (f_2) of EFV, FTC and TDF in four different dissolution media

Study Subjects

A total of 52 healthy Thai male volunteers were enrolled in the study. The mean ± SD of age, height, weight, and BMI of all subjects were 29.08 ± 7.46 years, 1.71 ± 0.06 m, 66.30 ± 8.04 kg, and 22.48 ± 2.04 kg/m^2, respectively. They were randomly and equally divided into two groups: reference-test (RT) and test-reference (TR) groups. There were 41 subjects completed the study. Six subjects were withdrawn as they met the conditions making them ineligible for dosing. Additional five subjects dropped out from the study due to personal reasons. However, one of them dropped out at nearly the end of the study. The data from this subject

were sufficient for pharmacokinetic calculation. Consequently, the data from 42 subjects were qualifiable for pharmacokinetic and statistical analysis.

Study Sample Analysis

A total of 2392 study samples were completely analyzed in the linear concentration range of 51.115-6028.004 ng/mL, 50.800-3006.228 ng/mL, and 10.373-804.835 ng/mL for EFV, FTC and TFV, respectively. The correlation coefficient calculated from 8 calibration standards of each analyte was more than 0.98 for all analytical runs. The precision and accuracy of the analysis were demonstrated using quality control samples in each analytical run. The inter-day precision and accuracy of quality control samples of all analytes were in the range of 3.4-8.7% of the coefficient of variation (CV) and 92.3-107.7% of nominal concentration, respectively. The analysis was completed within established long-term stability of 171 days.

Pharmacokinetic and Statistical Analysis

Mean plasma concentration-time profiles of EFV, FTC, and TFV after oral administration of the test and reference products are illustrated in Figure 1, 2 and 3, respectively. The mean ± SD values of the studied pharmacokinetic parameters for the test and reference products are summarized in Table 2 for EFV, Table 3 for FTC, and Table 4 for TFV.

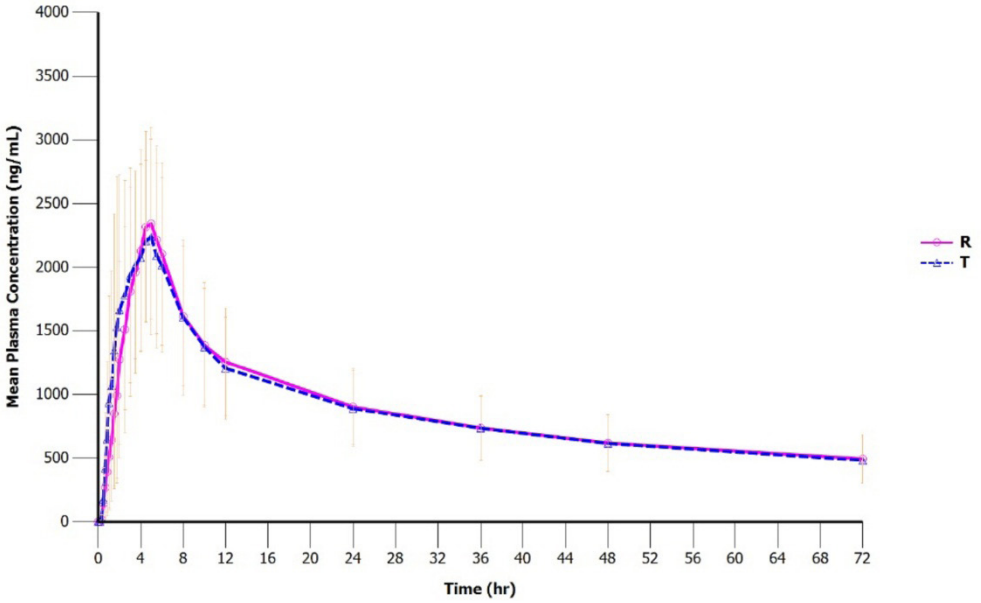

Figure 1: Plasma concentration time profiles of EFV after oral administration of the test (T) and reference (R) products. The data is mean ± SD, N=42.

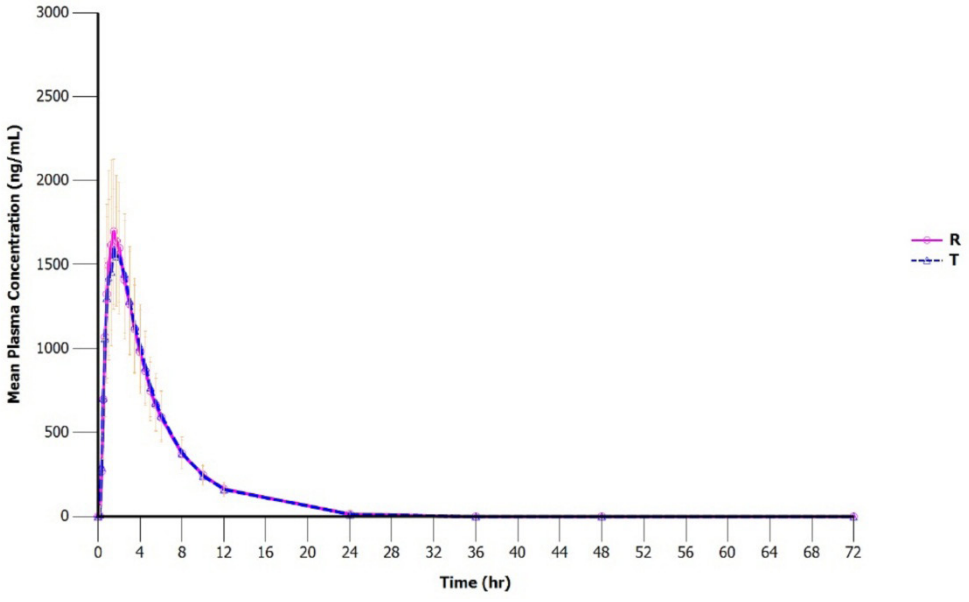

Figure 2: Plasma concentration time profiles of FTC after oral administration of the test (T) and reference (R) products. The data is mean ± SD, N=42.

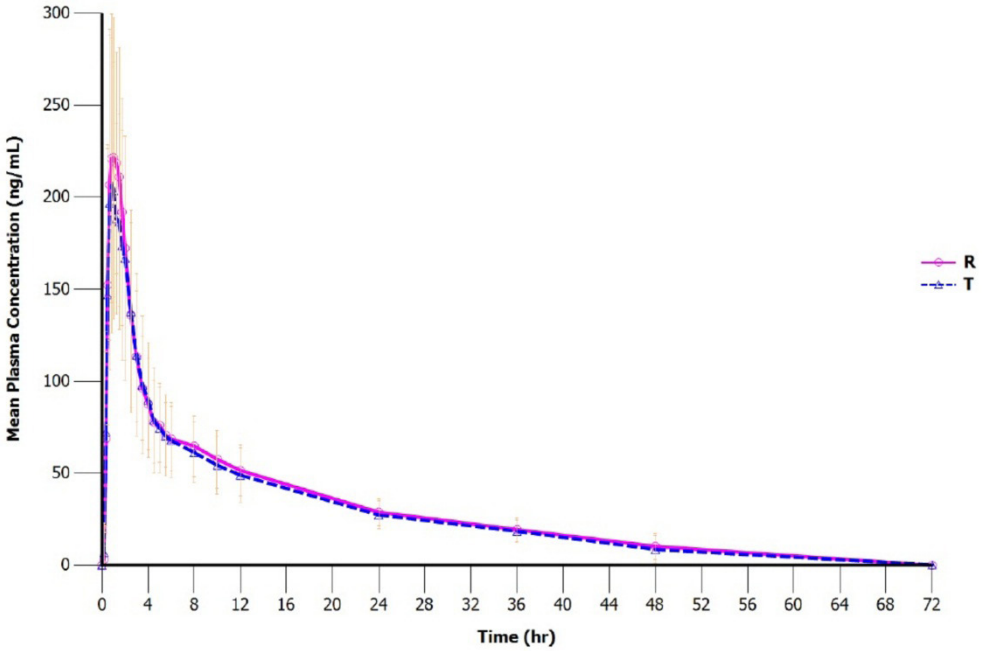

Figure 3: Plasma concentration time profiles of TFV after oral administration of the test (T) and reference (R) products. The data is mean ± SD, N=42.

Parameters	Mean ± SD		Ratio (90% CI)	Power	Intra-subject variability (% CV)
	Test product	Reference product			
AUC_{0-72} (ng.hr/mL)	62551 ± 18125	62312 ± 17728	100.7 (94.42 - 107.39)	100.0	17.6
C_{max} (ng/mL)	2608 ± 880	2645 ± 749	97.3 (88.82 - 106.56)	99.0	25.1
Median t_{max} (hr) (min,max)	4.000 (1.250,8.000)	4.500 (1.750,6.000)	-	-	-

Table 2: Pharmacokinetic parameters and statistical comparison for EFV

Parameters	Mean ± SD		Ratio (90% CI)	Power	Intra-subject variability (% CV)
	Test product	Reference product			
AUC_{0-72} (ng.hr/mL)	8705 ± 1630	8740 ± 1832	100.0 (95.55 - 104.62)	100.0	12.4
$AUC_{0-\infty}$ (ng.hr/mL)	9351 ± 1684	9407 ± 1803	99.6 (95.42 - 103.95)	100.0	11.7
C_{max} (ng/mL)	1808 ± 379	1868 ± 459	98.0 (92.74 - 103.59)	100.0	15.1
Median t_{max} (hr) (min,max)	1.50 (0.83,2.50)	1.50 (0.83,3.00)	-	-	-
λ_z	0.20 ± 0.06	0.19 ± 0.05	-	-	-
$t_{1/2}$	3.86 ± 1.55	3.94 ± 1.44	-	-	-
Extrapolated AUC (%)	6.99 ± 1.99	7.36 ± 2.35	-	-	-

Table 3: Pharmacokinetic parameters and statistical comparison for FTC

Parameters	Mean ± SD		Ratio (90% CI)	Power	Intra-subject variability (% CV)
	Test product	Reference product			
AUC_{0-72} (ng.hr/mL)	1912 ± 576	2009 ± 527	94.5 (88.86 - 100.50)	100.0	16.9
$AUC_{0-\infty}$ (ng.hr/mL)	2295 ± 626	2405 ± 584	94.8 (89.65 - 100.34)	100.0	15.4

C_{max} (ng/mL)	255 ± 71	271 ± 63	93.5 (86.85 - 100.65)	99.9	20.2
Median t_{max} (hr) (min,max)	1.000 (0.500,4.500)	1.000 (0.667, 2.500)	-	-	-
λ_z	0.04 ± 0.01	0.04 ± 0.01	-	-	-
$t_{1/2}$	18.20 ± 3.48	18.85 ± 4.74	-	-	-
Extrapolated AUC (%)	17.11 ± 4.31	16.77 ± 4.45	-	-	-

Table 4: Pharmacokinetic parameters and statistical comparison for TFV

Adverse event	Report adverse event incidence	
	Test product	Reference product
Gastrointestinal disorders		
Nausea	1	1
Loose stools	0	1
Eye disorders		
Blurred vision	1	0
Laboratory examinations		
Increasing of ALT, AST and alkaline phosphatase level	4	4
Increasing of total protein and albumin level	2	2
Increasing of eosinophil level	0	1
Nervous system disorders		
Dizziness	16	11
Total adverse events	**24**	**20**

Table 5: List of adverse events

Statistical analysis was performed on the data obtained from the subjects who provided evaluable data for both test and reference products (N=42). The results of ANOVA showed insignificant effect of sequence, period, and formulation on log-transformed AUC_{0-72}, $AUC_{0-\infty}$, and C_{max} of all analytes ($p > 0.05$). The 90% CIs for the geometric mean ratios of log-transformed AUC_{0-72}, $AUC_{0-\infty}$ and C_{max} between the test and reference formulations were within the acceptance range of 80.00-125.00% as presented in Table 2, 3 and 4 for EFV, FTC, and TFV, respectively. The Wilcoxon signed-rank test revealed no significant difference in t_{max} between the test and reference products for all three analytes ($p > 0.05$).

Tolerability

With concerning to the tolerability and welfare of study subjects, adverse event monitoring was performed closely during the study. A total of 44 adverse events were reported in 31 subjects as presented in Table 5. There were 24 adverse events reported in 22 subjects receiving the test formulation whereas 20 adverse events were reported in 15 subjects receiving the reference formulation. In 6 subjects, adverse events were experienced in both study periods. The most frequently reported adverse events were dizziness, followed by increasing of ALT, AST and alkaline phosphatase levels. The intensity of adverse events was assessed to be mild and could recover without any medical treatment.

Discussion

EFV is classified as low soluble drug (Biopharmaceutics Classification System; BCS class 2 or 4), whereas FTC and TDF are BCS class 1 and 3, respectively [9,10]. The dissolution medium requires 2% of SLS for EFV to achieve sink conditions [11]. The dissolution profiles of the test and reference formulations were similar in all tested media for FTC and TDF. However, only the dissolution profiles of EFV in phosphate buffer pH 6.8 + 2% SLS was accepted as similar. Since EFV is mainly absorbed in the intestine, the dissolution test in phosphate buffer pH 6.8 + 2% SLS supported the decision to proceed to *in vivo* bioequivalence study [12].

The plasma samples of each study subject from two study periods were analyzed altogether. Plasma concentration of all analytes were simultaneously determined by LC-MS/MS method which was validated as per the Guideline on bioanalytical method validation of European Medicines Agency (EMA) [13]. Plasma samples of subjects were assayed for EFV (lower limit of quantification, LLOQ = 51.115 ng/mL), FTC (LLOQ = 50.800 ng/mL) and TFV (LLOQ = 10.373 ng/mL) as per Product-Specific Guidances for Generic Drug Development, U.S. FDA [14] and Notes on the design of bioequivalence study, WHO [8]. For TDF, the active metabolite (TFV) was measured instead of parent compound due to rapid conversion of TDF to TFV after oral absorption and thus bioequivalence of TDF needs to be demonstrated using TFV [8,15]. The concentrations of calibration curve standards and

quality control samples used in this study were suitable for determination of the analytes since at least two quality control sample levels fell within the range of study samples concentrations of each analyte in each analytical run [13]. The precision and accuracy demonstrated by quality control samples in the run suggested reliability and reproducibility of the data.

In the present study, there were 6 withdrawn and 5 dropped out subjects in the study, however, one of these subjects dropped out at nearly the end of the study and the data were sufficient for subsequent data analysis. Therefore, the data from 42 subjects were used for pharmacokinetic and statistical analysis. This study was conducted in fasting conditions since EFV/FTC/TDF fixed-dose combination tablet was indicated to administer orally on an empty stomach [4]. From a pre-defined blood sampling time points over 72 hours after oral administration, the sampling time points were designed to collect blood sample at every 10 minutes in the first hour to capture the C_{max} in absorption phase due to rapid absorption of FTC and TDF. In addition, last blood sampling time point was at 72 hours after dosing and washout period was designed as at least 28 days because of long half-life of EFV [3,5].

Considering the data of three analytes, the pharmacokinetic profiles and pharmacokinetic parameters were comparable between the test and reference products. The $AUC_{0-\infty}$ was not calculated for EFV as the AUC was truncated at 72 hours. This period should cover the absorption phase of immediate release dosage form and could be used for bioequivalence assessment for long half-life drug [16]. Therefore, total sample collection period of 72 hours and truncated AUC at 72 hours were sufficient for bioequivalence evaluation of EFV. Moreover, C_{max} and t_{max} of all three analytes which obtained from this bioequivalence study were found to be comparable with the existing published study (Test/Reference; C_{max} of EFV; 2280/2300, C_{max} of FTC; 2130/2380, C_{max} of TFV; 325/353, t_{max} of EFV; 3.50/3.75, t_{max} of FTC; 1.50/1.50, t_{max} of TFV; 1.00/0.75) [17]. The powers of the tests conducted on AUC_{0-72}, $AUC_{0-\infty}$ and C_{max} were more than 90% suggesting that the data from 42 volunteers was adequate for bioequivalence evaluation. Wilcoxon signed-rank test demonstrated that there was no significant difference in median t_{max} values of EFV, FTC and TFV between the test and reference products ($p > 0.05$). Based on the results, the rate determined by C_{max} and t_{max} and the extent of absorption determined by AUC from the test and reference formulations were not significantly different.

The adverse event monitoring was performed closely throughout the study to evaluate the tolerability of the formulations on the basis of clinical and laboratory examinations. Both products were well tolerated by the study subjects. The incidence of adverse events reported after receiving the test and reference products was similar. All adverse events were possibly related to the study products as these adverse events are commonly found for the study drugs [3,5,7].

Conclusion

Based on statistical inferences, the test formulation (GPO-VIR T®) was bioequivalent to the reference formulation (Atripla®) in terms of rate and extent of absorption of EFV, FTC and TDF (demonstrated using TFV). Therefore, the products can be used interchangeably as the same efficacy and tolerability can be anticipated.

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