

# A PHASE I, OPEN-LABEL, SINGLE-DOSE, RANDOMIZED, CROSS-OVER STUDY OF GENICRIVIROC (CVC) AND TENOFOVIR (TDF) IN HEALTHY VOLUNTEERS

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## ABSTRACT

**Background:** CVC is a CCR5/CCR2 antagonist with potent antiretroviral activity in HIV-1-infected patients. In preparation for phase 2/3 studies, the pharmacokinetics (PK), safety, and tolerability of CVC and TDF were studied.

**Methods:** In this open-label, random sequence, cross-over study, 21 healthy volunteers received a single dose each of CVC 150 mg, TDF 300 mg, and CVC 150 mg + TDF 300 mg, with a washout of 14 days between regimens. PK profiles were obtained over a 7-day period after each treatment. Safety was assessed by AE, laboratory, and vital sign assessments; ECGs; and physical examinations.

**Results:** Coadministration of CVC and TDF did not affect the PK of CVC nor the AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> of TDF. The C<sub>max</sub> of TDF was increased approximately 36%, with 90% CIs outside the equivalence range, suggesting that CVC may affect the rate of absorption of TDF. The t<sub>1/2</sub> of TDF with and without CVC was 20.40 vs. 18.95 hours, respectively. Respective mean CL/F values of CVC alone and in combination with TDF were 17.0 L/h and 19.5 L/h and of TDF alone and in combination with CVC were 102 L/h and 78.2 L/h. CVC+TDF was well tolerated. There were no deaths, no study discontinuations, and no SAEs; all AEs were of mild intensity. Fewer AEs were reported with combination therapy than with either drug alone (2, 1, and 0 subjects with drug-related AEs on CVC, TDF, and CVC+TDF, respectively).

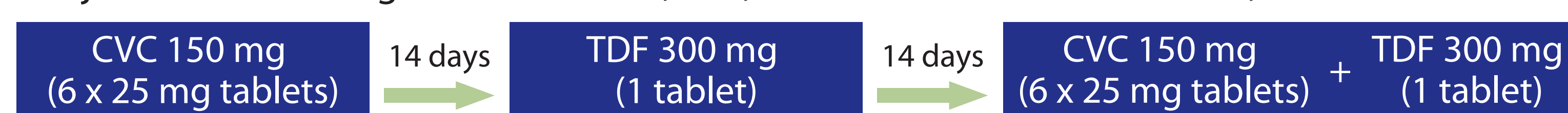
**Conclusions:** Coadministration of CVC and TDF did not affect the PK of CVC nor the AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> of TDF. Coadministration increased the C<sub>max</sub> of TDF, suggesting that CVC may affect the rate of absorption of TDF. There was no safety contraindication to the coadministration of CVC and TDF.

## BACKGROUND

CVC (TBR-652) is a CCR5/CCR2 antagonist with potent antiretroviral activity in HIV-1-infected patients.<sup>1</sup> The pharmacokinetics, safety, and tolerability of CVC and TDF coadministration were studied in preparation for a phase 2 study using CVC in combination with nucleoside/nucleotide analog reverse transcriptase inhibitors.

## METHODS

This was an open-label, random sequence, cross-over study to assess the PK, safety, and tolerability of CVC administered with and without TDF. The study population included adult men and women between ages 18 and 55 years old who had had no significant metabolic, endocrinologic, hepatic, renal, hematologic, pulmonary, cardiovascular, gastrointestinal, urologic, neurologic, or psychiatric disorders; had a body mass index (BMI) between 18 and 30 kg/m<sup>2</sup>; were willing to take appropriate precautions to prevent pregnancy; had no recent history (≤30 days) of clinically significant infection; had no positive serology indicative of hepatitis B or C or HIV infection; and had no clinically significant findings on screening evaluations. Subjects received single doses of CVC, TDF, or CVC/TDF in random order, as follows:



### Pharmacokinetic Analysis

A PK profile was obtained for CVC and TDF over a 7-day period following each dose, and individual plasma concentrations and PK parameters were summarized by descriptive statistics. The extent of a drug-drug interaction of TDF on the PK of CVC or CVC on the PK of TDF was estimated using a random analysis of variance (ANOVA) model performed on the log-normal (ln) transformed maximum plasma concentration (C<sub>max</sub>), area under the concentration-versus-time curve from predose to the last quantifiable concentration time point (AUC<sub>0-t</sub>), and AUC from time zero to infinity (AUC<sub>0-∞</sub>).

### Safety Analysis

Safety was assessed based on AE, laboratory, and vital sign assessments; ECGs; and physical examinations.

### Statistical Analysis

A mixed-effect ANOVA model with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect was applied to the transformed parameters. Calculations of least square (LS) means, differences between adjusted treatment LS means, and the standard error associated with these differences were deduced from this model. Statistical significance was assessed at the two-sided 5% level. The natural ln-transformed results were back-transformed to the original scale by exponentiation to obtain geometric LS means for each treatment and geometric LS mean ratios from the concomitant administration of CVC and TDF relative to the single administration of each, with 90% confidence intervals (CIs) around the ratios. Absence of a drug-drug interaction was assumed if the 90% CI around the ratio lay within the equivalence range of 70% to 143%. Steady-state concentrations of TDF with CVC were predicted using nonparametric superposition.

## RESULTS

### Demographics/Disposition

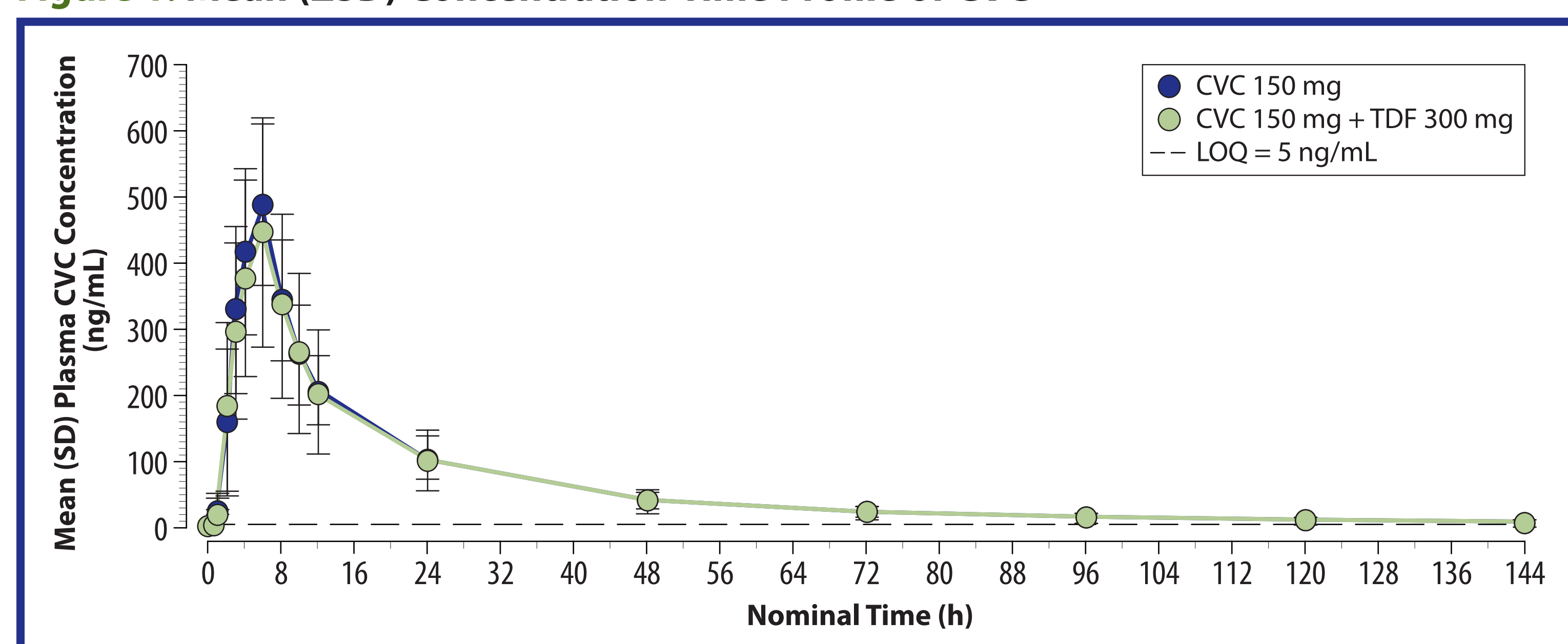
21 subjects were enrolled: 8 females and 13 males; 17 whites and 4 blacks. Three of the 21 subjects were Hispanic/Latino. Median age was 33 years old (range, 21-53 years). Median BMI was 25 kg/m<sup>2</sup> (range, 21-29 kg/m<sup>2</sup>). All dosing was confirmed by direct observation, and all subjects received all doses.

**Table 1. Noncompartmental Pharmacokinetic Parameters for CVC and TDF Administered Alone and Together**

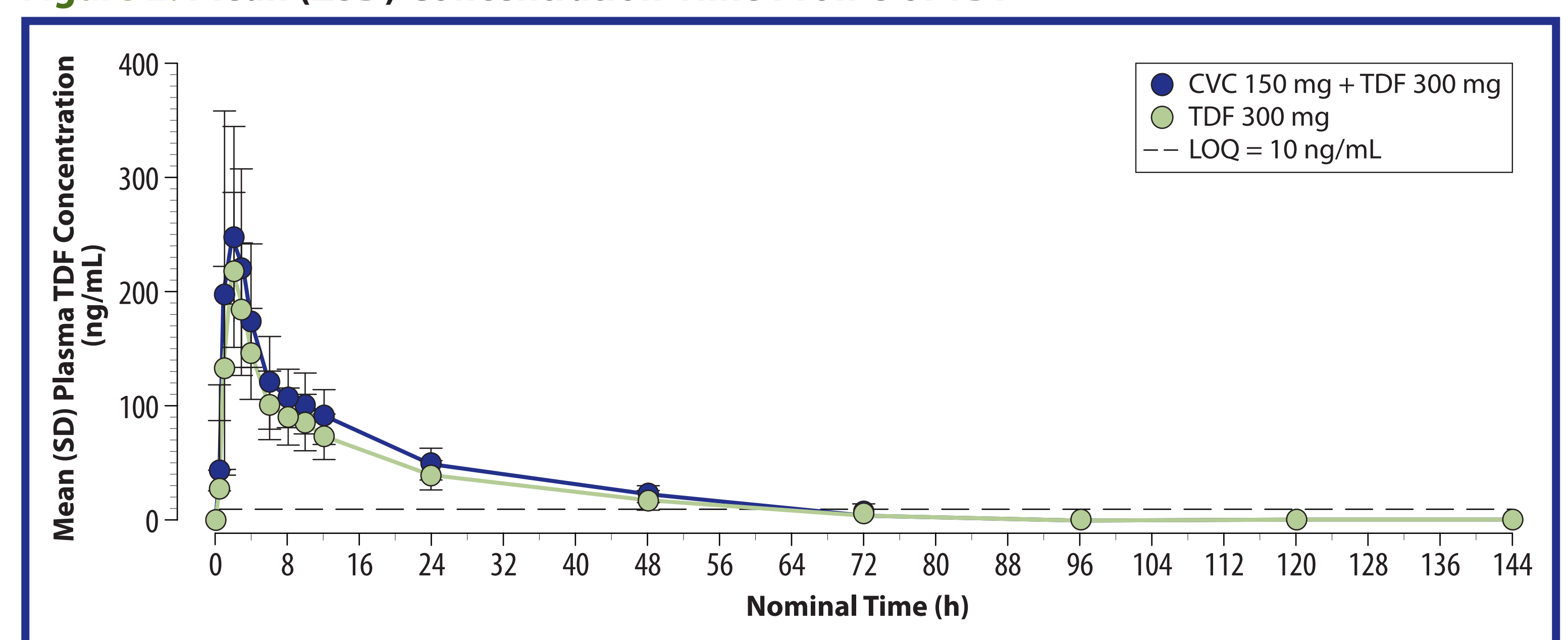
Parameter	Arithmetic Mean (CV%)			
	CVC		TDF	
	Alone (N=21)	With TDF (N=21)	Alone (N=21)	With CVC (N=21)
AUC <sub>0-t</sub> (ng·h/mL)	8969 (28.3)	8523 (41.2)	2794 (34.0)	3597 (26.0)
AUC <sub>0-∞</sub> (ng·h/mL)	9628 (29.9)	9168 (42.0)	3235 (32.0)	4046 (24.3)
C <sub>max</sub> (ng/mL)	494 (25.7)	455 (37.3)	244 (22.7)	332 (26.3)
t <sub>lag</sub> (h) <sup>a</sup>	0.50 (0.00, 2.00)	0.50 (0.00, 2.00)	0.50 (0.00, 1.00)	0.50 (0.00, 2.00)
t <sub>max</sub> (h) <sup>a</sup>	6.00 (4.00, 6.00)	6.00 (3.00, 10.02)	2.00 (0.50, 3.00)	2.00 (0.50, 4.00)
t <sub>1/2</sub> (h)	49.68 (28.2)	48.66 (31.1)	18.95 (24.8)	20.40 (22.6)
CL/F (L/h)	17.0 (30.8)	19.5 (44.2)	102 (31.7)	78.2 (23.7)

<sup>a</sup> Median (minimum, maximum)

**Figure 1. Mean (±SD) Concentration-Time Profile of CVC**



**Figure 2. Mean (±SD) Concentration-Time Profile of TDF**



**Table 2. Drug-Drug Interaction Assessment**

Parameter	Test CVC+TDF	Geometric LS Mean		
		Reference CVC or TDF	Ratio of LS Means Test: Reference (%)	90% CI
Effect of TDF on CVC Values				
AUC <sub>0-t</sub> (ng·h/mL)	7793	8610	90.5	81.4, 101
AUC <sub>0-∞</sub> (ng·h/mL)	8383	9225	90.9	81.8, 101
C <sub>max</sub> (ng/mL)	420	475	88.4	80.0, 97.6
Effect of CVC on TDF Values				
AUC <sub>0-t</sub> (ng·h/mL)	3491	2643	132	123, 141
AUC <sub>0-∞</sub> (ng·h/mL)	3945	3081	128	120, 136
C <sub>max</sub> (ng/mL)	324	239	136	125, 148

### PK Summary

- The ratios of geometric LS means for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> of CVC were 90.5%, 90.9%, and 88.4%, respectively (**Table 2**). The absence of drug-drug interaction with TDF, confirmed by the 90% CIs around the ratio of LS mean values completely contained within the equivalence range.
- No drug-drug interactions were observed for AUC parameters of TDF since ratios of LS means and 90% CIs for AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> were within the equivalence range (**Table 2**).
- The 90% CI for C<sub>max</sub> of TDF fell outside the equivalence range (**Table 2**), which was attributed to changes in absorption rather than elimination. This hypothesis was supported by the similar t<sub>1/2</sub> observed when TDF was administered with and without CVC (20.40 vs. 18.95 h, respectively) (**Table 1**).
- A moderate accumulation of TDF (AUC<sub>0-24</sub>) was estimated for multiple once-daily oral administration of TDF alone and in combination with CVC, as indicated by the accumulation factor of approximately 1.5.
- Overall, drug-drug interactions under steady-state conditions should be similar to those observed after single dose administration.

### Safety

**Table 3. Overall Treatment-Emergent Adverse Events by System-Organ-Class**

System Organ Class Preferred Term <sup>a</sup>	CVC (N=21)	TDF (N=21)	CVC+TDF (N=21)
Subjects with at least 1 TEAE <sup>b</sup>	4 (19.0%)	4 (19.0%)	2 (9.5%)
Gastrointestinal disorders	2 (9.5%)	0	0
Diarrhoea	1 (4.8%)	0	0
Vomiting	1 (4.8%)	0	0
General disorders and administration site conditions	0	1 (4.8%)	0
Facial pain	0	1 (4.8%)	0
Infections and infestations	1 (4.8%)	1 (4.8%)	1 (4.8%)
Nasopharyngitis	1 (4.8%)	1 (4.8%)	1 (4.8%)
Musculoskeletal and connective tissue disorders	0	1 (4.8%)	0
Pain in extremity	0	1 (4.8%)	0
Nervous system disorders	2 (9.5%)	2 (9.5%)	0
Headache	2 (9.5%)	2 (9.5%)	0
Reproductive system and breast disorders	0	1 (4.8%)	0
Dysmenorrhoea	0	1 (4.8%)	0
Respiratory, thoracic and mediastinal disorders	1 (4.8%)	0	1 (4.8%)
Nasal congestion	0	0	1 (4.8%)
Oropharyngeal pain	1 (4.8%)	0	0

<sup>a</sup> Multiple events in the same preferred term for a subject are only counted once in the statistics of that system organ class.

<sup>b</sup> A treatment-emergent adverse event (TEAE) is an AE that occurred on or after the first dose of study drug or worsened after the first dose of the study, including AEs that occurred during follow-up.

### Safety Summary

- There were no deaths, no discontinuations for AEs, and no SAEs.
- All AEs were reported as mild. Only 4 AEs in 3 patients were considered possibly related to study drug and resolved rapidly; none were considered probably or definitely related to study drug.
- The combination of CVC plus TDF resulted in fewer treatment-emergent AEs than either CVC or TDF alone (**Table 3**).
- There was a single, isolated grade 3 partial thromboplastin time (PTT) elevation on Day 2 of TDF dosing, which resolved without sequelae. PTT was within normal range at all other times.
- There were no clinically significant or grade 4 laboratory, physical examination, vital signs, or ECG events.

## CONCLUSIONS

- Coadministration of CVC and TDF did not affect the PK of CVC.
- Coadministration of CVC and TDF did not affect the AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> of TDF, the C<sub>max</sub> of TDF was increased by approximately 36%, suggesting that CVC may affect the rate of absorption of TDF. Similar conclusions were obtained when assessing the effect of CVC on the steady-state C<sub>max</sub> of TDF.
- No dose adjustments are necessary when CVC and TDF are co-administered.
- There was no safety contraindication to the administration of CVC in combination with TDF.

## REFERENCE

- Lalezari J, Gathe J, Brinson C, et al. Safety, Efficacy, and Pharmacokinetics of TBR 652, a CCR5/CCR2 Antagonist, in HIV 1-Infected, Treatment-Experienced, CCR5 Antagonist-Naïve Subjects. *J Acquir Immuno Defic Syndr* 2011 Feb 11 [Epub ahead of print].

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