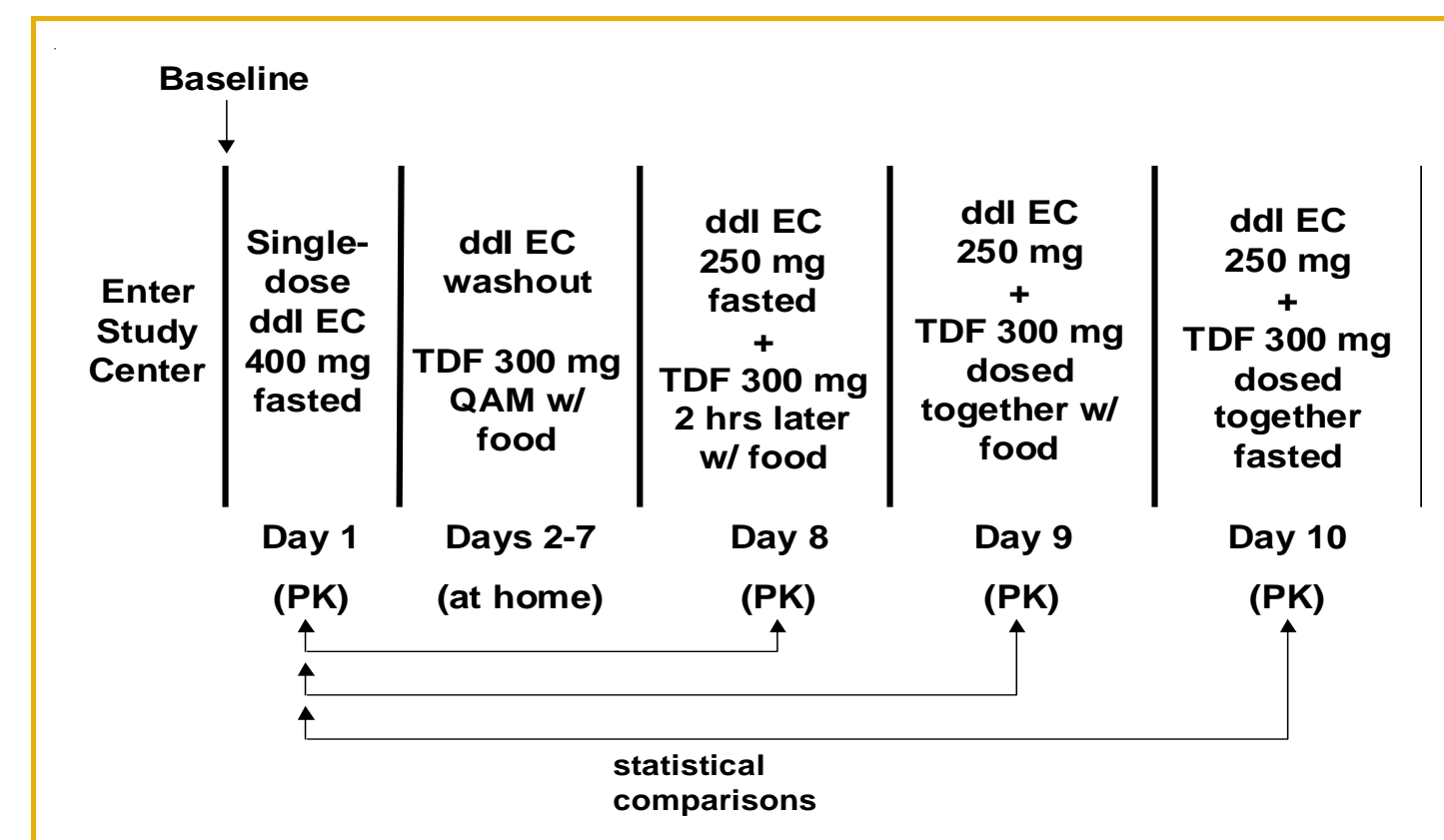


**Introduction**

- Tenofovir disoproxil fumarate (TDF) is a single tablet, once-daily nucleotide reverse transcriptase inhibitor for treatment of HIV-1 infection
- Didanosine (ddI), available as a buffered tablet (Videx®) and the encapsulated enteric-coated beadlet formulation (Videx EC), can be administered once daily
- Administration of tenofovir DF and didanosine together is attractive as both are once-daily therapies
- Previous pharmacokinetic studies<sup>1,2</sup> have shown tenofovir exposure is not impacted by didanosine but that there is increased systemic didanosine exposure of 44 - 60% when didanosine buffered tablet or enteric-coated capsule formulations are coadministered with tenofovir DF
- These increases are such that when used in combination with TDF a ddI dose reduction may be appropriate to target a systemic exposure comparable to ddI 400 mg alone

**Objectives**

- Evaluate ddI pharmacokinetics when ddI EC 250 mg is administered in the fasted state and TDF is administered with a light meal per current dosage and administration instructions (regulatory labeling)
- Evaluate ddI pharmacokinetics following simultaneous co-administration of ddI EC 250 mg and TDF in both the fasted and fed state

**Figure 1. Study Design****Methods****Study Design**

- Phase 1, open-label, multiple-dose, one-sequence, drug-drug interaction study of TDF 300 mg and ddI EC 250 mg compared to ddI EC 400 mg alone in healthy male and female subjects ( $\geq 60$  kg)
- Subjects received the following treatments:  
Day 1: ddI EC 400 mg (fasted)  
Day 2-7: TDF 300 mg with morning meal  
Day 8: ddI EC 250 mg (fasted) + TDF 300 mg (2 hours later with light meal)  
Day 9: ddI EC 250 mg + TDF 300 mg together with light meal  
Day 10: ddI EC 250 mg + TDF 300 mg together (fasted)
- Standardized light meal (~373 kcal, ~20% fat) administered prior to TDF dosing at pharmacokinetic visits on Days 8 and 9
- Blood samples collected over 24 hours following the administration of study drugs on Days 1, 8, 9, and 10
- Samples assayed by a validated LC/MS/MS assay
  - Tenofovir standard curve range 3-600 ng/mL
  - Didanosine standard curve range 0.5-500 ng/mL

**Pharmacokinetic and Statistical Analysis**

- Pharmacokinetic parameters were calculated by a noncompartmental method using the WinNonlin® pharmacokinetic software package and the linear/log trapezoidal rule
- The ratio of geometric means for AUC and Cmax and their 90% confidence intervals (CI) were derived for each drug when administered alone or together using a Mixed Model Analysis
- No alteration in the pharmacokinetics was concluded if the limits of the 90% CI around the ratio of geometric means (GMR) for  $AUC_{0 \rightarrow t}$  and Cmax was encompassed by the pharmacokinetic-equivalence bounds of 80% to 125%

**Safety Analyses**

- Routine adverse event and laboratory monitoring

**Results****Table 1. Demographic Characteristics of Healthy Subjects (n=28)**

Age (yr) <sup>a</sup>	28 (7)
Weight (kg) <sup>a</sup>	79.2 (9.4)
Gender (M/F)	17/11
Race (Caucasian/Non-Caucasian)	24/4

<sup>a</sup>Mean (SD)**Table 2. Pharmacokinetic Results**

Regimen	ddI Cmax <sup>a</sup> ( $\mu\text{g/mL}$ )	GMR <sup>b</sup> (90% CI)	ddI AUC <sup>a</sup> ( $\mu\text{g}\cdot\text{hr/mL}$ )	GMR <sup>b</sup> (90% CI)
ddI EC 400mg Alone	1.18	-	2.75	-
<b>ddI EC 250mg + TDF:</b>				
-Staggered (2hr prior)	1.06	89.5 (78.1, 103)	2.74	99.8 (89.2, 112)
-Simultaneous + Light Meal	0.84	71.1 (61.3, 82.4)	2.44	88.6 (76.8, 102)
-Simultaneous Fasted	1.09	92.4 (81.2, 105)	3.14	114 (100, 131)

<sup>a</sup>Geometric means<sup>b</sup>Relative to 400 mg alone**Safety Analyses**

- No serious adverse events or clinically significant laboratory abnormalities occurred during the conduct of the study
- A total of 76 clinical adverse events were reported in 18 (64%) of the 28 patients dosed
- Most clinical adverse events were mild to moderate in severity, except one patient that had Grade 3 hostility, nausea, and headache
- The clinical adverse events did not differ substantially for drugs given alone versus together

**Conclusions**

- Staggered administration (per regulatory labeling) of ddI EC 250 mg + TDF resulted in an AUC equivalent to ddI EC 400 mg alone
- Simultaneous co-administration of ddI EC 250 mg with TDF in the fasted and fed states resulted in slightly higher (+14%) and lower (-11%) ddI AUCs, respectively
- Administration of ddI EC 250 mg with TDF staggered or simultaneously with or without a meal results in similar drug exposures to ddI EC 400 mg alone

**References**

<sup>1</sup>Kearney B, Damle B, Plummer A., et al. Tenofovir DF (TDF) and Didanosine EC (ddI EC): Investigation of Pharmacokinetic (PK) Drug-Drug and Drug-Food Interactions. The XIV International AIDS Conference; 2002 Jul 7-12; Barcelona, Spain.

<sup>2</sup>Flaherty J, Kearney B, Wolf J, et al. Coadministration of Tenofovir DF (TDF) and Didanosine (ddI): a Pharmacokinetic (PK) and Safety Evaluation. The 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Dec 16-19; Chicago, Illinois.