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Pharmacokinetic Evaluation of Reduced Doses of Didanosine Enteric Coated Capsules (ddI-EC) in Combination with Tenofovir Disoproxil Fumarate (TDF) and Food for a Once-Daily Antiretroviral Regimen

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INTRODUCTION

- The recommended once-daily dose of didanosine (ddI), a nucleoside reverse transcriptase inhibitor, in HIV-infected subjects with creatinine clearance ≥60 mL/min is 400 mg for subjects ≥60 kg and 250 mg for subjects <60 kg. Available strengths of ddI-EC are 125, 200, 250, and 400 mg.
- Previous studies indicate that coadministration of ddI-EC and TDF results in an increase in ddI exposures, but the exposures of TDF are unaltered.[1,2]
- Administration of 400 mg ddI chewable/dispersible buffered tablets and 300 mg TDF under fasted conditions resulted in a 44% increase in ddI AUC.[1]
- Administration of 400 mg ddI-EC under fasted conditions 2 h before 300 mg TDF and a light meal resulted in a 50% increase in ddI AUC. The increase in ddI AUC was 60% when 400 mg ddI-EC was coadministered with 300 mg TDF and a light meal.[2]
- An increase in systemic exposure may increase the risk of ddI associated toxicities. Therefore, the dose of ddI needs to be reduced when used in combination with TDF.
- The purpose of this study is to identify ddI-EC doses, in combination with TDF, that will result in ddI exposures comparable to 400 or 250 mg ddI-EC given alone in the fasted state.

OBJECTIVES

- To determine the pharmacokinetics of ddI following coadministration of 250 or 325 mg ddI-EC with 300 mg of TDF and food, relative to 400 mg ddI-EC under fasted conditions.
- To determine the pharmacokinetics of ddI following coadministration of 200 mg ddI-EC with 300 mg of TDF and food, relative to 250 mg ddI-EC under fasted conditions.
- To assess the acute safety of ddI-EC and TDF when administered alone or in combination.

METHODS

- Open-label, randomized, crossover study in 36 healthy subjects weighing ≥60 kg.
- On Days 1 and 3, subjects received a single dose of 250 or 400 mg ddI-EC in the fasted state in a randomized crossover manner.
- On Days 4-14, subjects received 300 mg TDF once daily with a light meal (373 kcal from 68% carbohydrate, 20% fat, and 12% protein). In addition, a single dose of 200, 250, or 325 mg ddI-EC was coadministered on Days 10, 12, and 14 in a randomized crossover manner.
- Serial blood samples were collected on Days 1, 3, 10, 12, and 14 at pre-dose and up to 24 hours post-dose.
- Plasma samples were assayed for ddI by a validated LC/MS/MS method.
- Single dose pharmacokinetic parameters of ddI were derived using a non-compartmental analysis.
- Absence of drug interaction was concluded if the 90% confidence interval (CI) for the ratio of test to reference geometric means fell within 0.80-1.25 interval for AUC and C_{max}.
- Clinical safety evaluations were performed at screening, during, and prior to discharge from the study.

RESULTS

- This study enrolled 36 subjects, of which 33 completed the study.
  - One subject discontinued for a personal reason.
  - One subject was discontinued by the Investigator due to a concussion to his head resulting from a physical assault during furlough (unrelated to study drug).
  - One subject discontinued due to vomiting and nausea (possibly related to study drug).
- There were no deaths or other serious adverse events (SAEs).
- The most frequently reported AEs (in more than 10% of the subjects) were nausea (22.9%), vomiting (11.4%), and rash (11.4%), all of which occurred during administration of TDF alone (Days 4-10).
- All AEs, except one (concussion, rated as severe), were mild or moderate in intensity and were resolved.

Table 1. Baseline Demographic Characteristics

Mean Age, years (Range)	30 (19-45)
Gender, N (%)	
Male	31 (86)
Female	5 (14)
Race, N (%)	
White	28 (78)
Black	6 (16)
Asian/Pacific Islander	1 (3)
Other (American Indian)	1 (3)
Mean Weight, kg (Range)	81.6 (60.8-99.0)
Mean Height, cm (Range)	180.9 (160.0-200.7)
Mean Body Mass Index, kg/m^2 (Range)	25.2 (19.1-30.0)

RESULTS cont'd

Comparison of 250 or 325 mg ddI-EC with TDF and Light Meal Relative to 400 mg ddI-EC Fasted

Figure 1. Mean (SD) Plasma Concentration-Time Profiles of ddI

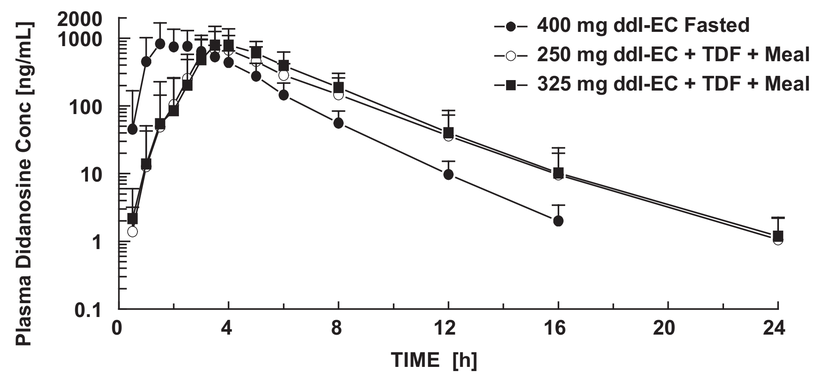

Table 2. Geometric Means and Point Estimates (90% CI) for C_{max} and AUC of ddI

Parameter (units)	Treatment	Adjusted Geometric Mean	Ratio of Adjusted Geometric Means Point Estimate (90% CI)
C_{max} (ng/mL)	400 mg ddI-EC Fasted (reference)	1106.4	---
	250 mg ddI-EC + TDF + Meal	881.8	0.797 (0.680, 0.934)
	325 mg ddI-EC + TDF + Meal	981.0	0.887 (0.756, 1.039)
AUC (ng·h/mL)	400 mg ddI-EC Fasted (reference)	2803.9	---
	250 mg ddI-EC + TDF + Meal	2671.3	0.953 (0.868, 1.046)
	325 mg ddI-EC + TDF + Meal	3175.8	1.133 (1.032, 1.244)

Comparison of 200 mg ddI-EC with TDF and Light Meal Relative to 250 mg ddI-EC Fasted

Figure 2. Mean (SD) Plasma Concentration-Time Profiles of ddI

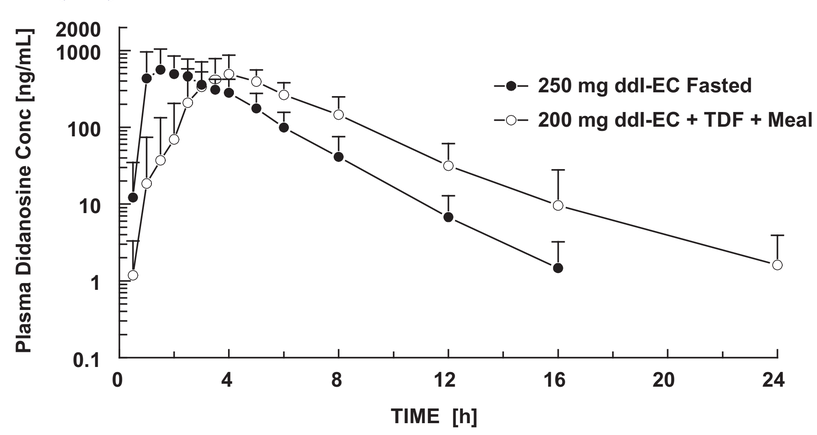

Table 3. Geometric Means and Point Estimates (90% CI) for C_{max} and AUC of ddI

Parameter (units)	Treatment	Adjusted Geometric Mean	Ratio of Adjusted Geometric Means Point Estimate (90% CI)
C_{max} (ng/mL)	250 mg ddI-EC Fasted (reference)	739.0	---
	200 mg ddI-EC + TDF + Meal	649.4	0.879 (0.750, 1.030)
AUC (ng·h/mL)	250 mg ddI-EC Fasted (reference)	1892.2	---
	200 mg ddI-EC + TDF + Meal	2192.1	1.159 (1.055, 1.272)

DISCUSSION/CONCLUSIONS

- In this study, 250 or 325 mg ddI-EC coadministered with 300 mg TDF and food resulted in ddI exposures bioequivalent to 400 mg ddI-EC fasted. This is consistent with a previous report indicating that 250 mg ddI-EC coadministered with 300 mg TDF and food resulted in ddI AUC similar to 400 mg ddI-EC fasted.[3]
- Administration of 200 mg ddI-EC with TDF and food resulted in ddI exposure similar to 250 mg ddI-EC fasted.
- C_{max} of ddI was lowered by 11-20% when coadministered with TDF and food, but is not felt to be clinically relevant.
- Didanosine EC and TDF were generally safe and well-tolerated when administered alone or in combination in normal healthy subjects.

REFERENCES

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