The Effect of Fostemsavir on the Pharmacokinetics of a Combined Oral Contraceptive (OC) Containing Ethinyl Estradiol (EE) and Norethindrone (NE) in Healthy Female Subjects

MOPEB0339

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Introduction

- Fostemsavir (FTR) is a prodrug of temsavir (TMR), a first-in-class attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T cells[1,2]

Study Rationale

- Women of childbearing potential represent a significant proportion of the heavily treatment-experienced HIV-1-infected population; evaluation of drug interaction potential between oral contraceptive (OC) and FTR is important

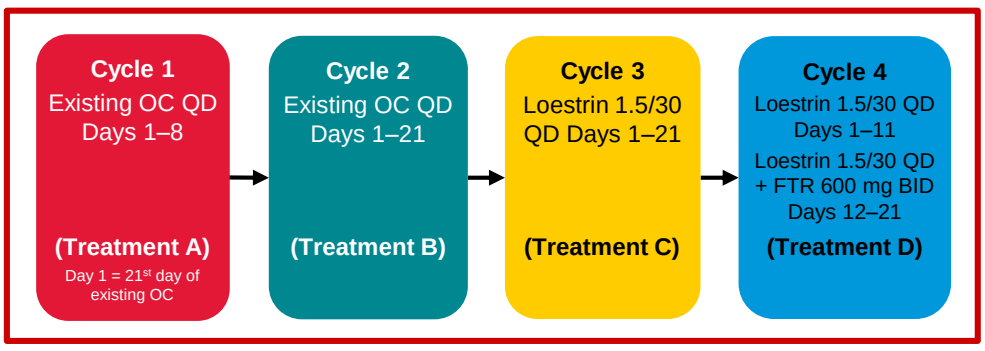
Objectives

- This study assessed the impact of FTR, administered twice daily (BID) as an extended-release (ER) tablet formulation, on the pharmacokinetics (PK) of a combined OC containing ethinyl estradiol (EE) and norethindrone (NE) (Loestrin 1.5/30 once daily (QD); 1.5 mg NE, 30 mcg EE) and on progesterone (a biomarker of ovulation) serum concentrations

Methods

- AI438019 was a Phase I, open-label, single-sequence, 4-cycle, 4-treatment study in 26 female subjects of childbearing potential, 18–40 years of age with a BMI of 18.0–32.0 kg/m^2 (**Figure 1**)
  - HIV-positive, HBV-positive and HCV-positive subjects were excluded

Figure 1. AI438019 Study Design



Assessments

- PK assessments: Serial blood samples for PK analysis were collected up to 24 hours post-dose on Days 10 and 21 of Cycle 3 and Day 21 of Cycle 4 for EE and NE. Plasma concentrations were quantified by validated LC/MS/MS methods. Non-compartmental PK parameters were derived from plasma concentration versus time data
  - Only comparisons of EE and NE PK on Day 21 between Treatments C and D are presented
- Pharmacodynamics: Blood samples for progesterone, a marker of ovulation suppression, were collected on Day 1 of Cycle 1, Day 21 of Cycle 2 and Days 11, 15 and 21 of Cycles 3 and 4
  - Progesterone level of 300 ng/dL provided a benchmark to identify if ovulation occurred in study subjects[3]
- Statistical analysis: A linear mixed-effect model with treatment, day and treatment-by-day as fixed effects and measurements within each subject as repeated measures, was fitted to the log-transformed Cmax and AUC(0-tau) to calculate geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for EE and NE
- Safety measures: Adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs) and physical examinations were recorded throughout the study

Results

Subject Disposition/Demographics

- 26 subjects were treated and 20 completed the study. Of the treated subjects:
  - Median (range) age was 30.6 (21–40) years
  - The majority of the subjects were White: 20 (76.9%)

Safety

- Two subjects had serious AEs (SAEs) during this study and both led to discontinuation of study therapy but were considered unrelated to study drug
  - One subject had a seizure during Treatment C (prior to FTR administration)
  - One subject had a spontaneous abortion reported >30 days after subject's last dose on Treatment B Day 1. Prior to the SAE, the subject was deemed unreliable and was discontinued from the study by the investigator. The subject did not receive FTR
- There were four subjects with laboratory-related AEs; all were mild in intensity, unrelated to study drug and resolved by the end of the study
- There were no deaths, no clinically significant findings based upon ECG abnormalities, vital sign measurements or physical examination findings

Pharmacokinetics

- Coadministration of combined OC containing EE and NE with FTR 600 mg ER BID increased EE exposure by approximately 40% (**Figure 2a, Table 1**)
- Coadministration of combined OC containing EE and NE with FTR 600 mg ER BID did not have meaningful impact on NE PK (**Figure 2b, Table 1**)
  - The 90% CIs of GMR of AUC(0-tau) and Cmax were within the bioequivalence range of 0.80–1.25
- There was no apparent change in the median Tmax of EE or NE when Loestrin 1.5/30 was coadministered with FTR at steady state

Pharmacodynamics

- As there was no difference in the overall number of subjects with serum progesterone ≥300 ng/dL across the cycles, it appeared there was no apparent effect of FTR on the ability of Loestrin 1.5/30 to inhibit ovulation (**Table 2**)

Figure 2. Mean (±SD) Plasma Concentration-time Profiles for EE (a) and NE (b) With and Without FTR

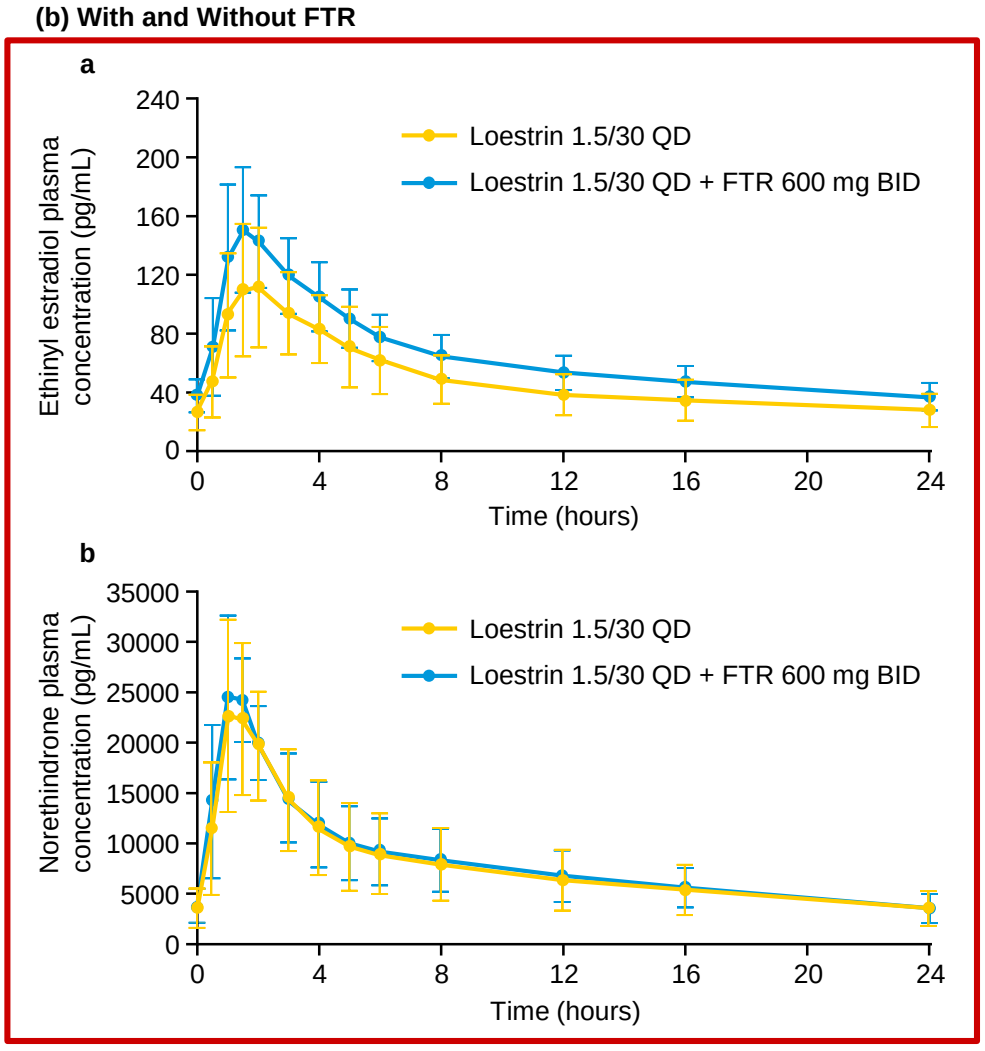


Table 1. Effect of FTR 600 mg ER BID on EE and NE PK

		Geometric mean (%CV)		GMR (90% CI)
Analyte	**Parameter**	**Treatment C, D21**	**Treatment D, D21**	**Treatment D vs C**
EE	Cmax	108 (39)	147 (27)	1.39 (1.28, 1.51)
	AUC(0-tau)	1083 (36)	1496 (22)	1.40 (1.29, 1.51)
	Tmax	2.00 (1.00–4.00)	1.50 (1.00–2.00)	
NE	Cmax	23629 (32)	25477 (24)	1.08 (1.01, 1.16)
	AUC(0-tau)	170293 (41)	184508 (20)	1.08 (1.03, 1.14)
	Tmax	1.00 (1.00–3.00)	1.00 (1.00–1.50)	

Cmax units = pg/mL; AUC(0-tau) units = pg*h/mL.
Treatment C, Loestrin 1.5/30 QD on Days 1–21; Treatment D, Loestrin 1.5/30 QD on Days 1–11, Loestrin 1.5/30 QD + FTR 600 mg BID on Days 12–21.

Table 2. Categorical Summary of Progesterone Results by Cycle

		Treatment sequence ABCD N (% of subjects)	
Cycle	**n[1]**	**<300 ng/dL**	**≥300 ng/dL[2]**
1	26	25 (96.2%)	1 (3.8%)
2	24	22 (91.7%)	2 (8.3%)
3	23	22 (95.7%)	1 (4.3%)
4	20	19 (95.0%)	1 (5.0%)

[1]n, number of subjects with non-missing results. [2]These subjects are five different subjects.
Treatment A, Existing OC QD on Days 1–8; Treatment B, Existing OC QD on Days 1–21; Treatment C, Loestrin 1.5/30 QD on Days 1–21; Treatment D, Loestrin 1.5/30 QD on Days 1–11, Loestrin 1.5/30 QD + FTR 600 mg BID on Days 12–21.

Conclusions

- Coadministration of FTR 600 mg ER BID with Loestrin 1.5/30 QD resulted in a modest 40% increase in EE exposure, no change in NE exposure
- FTR did not appear to affect the ability of Loestrin 1.5/30 to suppress ovulation based on serum progesterone results
- FTR will not impact the efficacy of combined EE and NE oral contraceptives
- FTR may be coadministered with combined oral contraceptives containing NE and ≤30 mcg of EE
- There are no data currently available on the use of FTR and combined oral contraceptives containing NE and EE in the presence of pharmacoenhancers

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Disclosure: Timothy Eley was employed by Bristol-Myers Squibb at the time of study conduct and analysis. He is now an employee of Arbutus Biopharma.

References: 1. Brown J, et al. *J Pharm Sci*. 2013;102:1742–1751. **2.** Langley DR, et al. *Proteins*. 2015;83:331–350. **3.** National Institute of Health Progesterone Test Reference Ranges. http://cclnprod.cc.nih.gov/dlm/testguide.nsf/Index/CB26894E1EB28DEF85256BA5005B000E.