The Effect of Fostemsavir on Methadone and Buprenorphine Pharmacokinetics

MOPEB0338

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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]
- A Phase III trial (NCT02362503) evaluating FTR 600 mg twice daily (BID) as an extended-release (ER) tablet formulation for use in HIV-1-infected, heavily treatment-experienced adults who have two or fewer active antiretroviral classes remaining due to resistance, intolerabilities, and/or contraindications is ongoing

Study Rationale

- Methadone and buprenorphine are used for treatment in people with opioid dependence, of which a significant proportion are infected with HIV[3]
  - Methadone consists of a racemic mixture, with R-methadone as the pharmacologically active enantiomer. Multiple cytochrome P450 (CYP) enzymes play a role in its disposition; however, recent data have suggested that CYP2B6 is the primary enzyme that metabolizes methadone, with CYP3A4 playing a minor role[4]
  - Buprenorphine is metabolized by CYP3A4, and both buprenorphine and its metabolite norbuprenorphine are further metabolized by glucuronidation

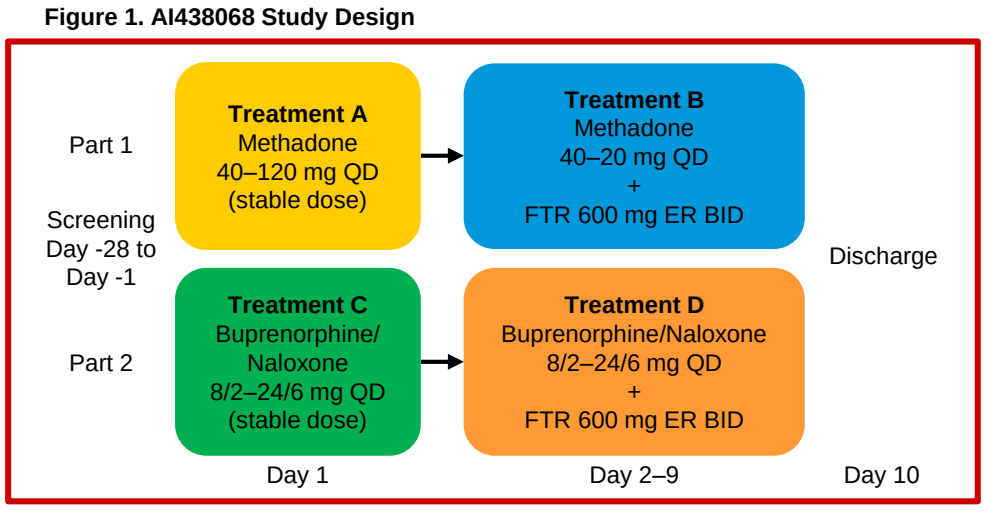
Objectives

- This study assessed the impact of FTR on the pharmacokinetics (PK) of the opioids methadone (R-, S-, and total) or buprenorphine/norbuprenorphine when coadministered

Methods

- AI438068 was a Phase I, open-label study in male and female subjects 18–65 years of age with a BMI of 18.0–34.0 kg/m^2 on methadone maintenance therapy (Part 1, N=16) or buprenorphine/naloxone maintenance therapy (Part 2, N=16) (**Figure 1**)
  - HIV- and HBV-positive subjects were excluded; a positive test for HCV antibodies with documentation of anti-HCV therapy was acceptable

Figure 1. AI438068 Study Design



Assessments

- PK assessments: Serial blood samples for PK analysis were collected up to 24 hours post-dose on Day 1 and Day 9 for methadone and buprenorphine and up to 12 hours post-dose on Day 9 for TMR. Plasma concentrations were quantified by validated LC/MS/MS methods. Non-compartmental PK parameters were derived from plasma concentration versus time data
- Pharmacodynamics: The potential effect of FTR 600 mg ER BID on the overdose and withdrawal effect of methadone and buprenorphine/naloxone was assessed using the Clinical Opiate Withdrawal Scale (COWS), the Subjective Opiate Withdrawal Scale (SOWS), the Objective Opiate Withdrawal Scale (OOWS), and the Opiate Overdose Assessment (OOA)
- Statistical analysis: A linear mixed-effect model with treatment as a fixed effect and measurements within each subject as repeated measures was fitted to the log-transformed Cmax, AUC(0-tau), and C24 to calculate geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for dose-normalized methadone (R-, S-, total), buprenorphine and norbuprenorphine
  - The effect of FTR was deemed clinically insignificant if the 90% CI fell within 0.70–1.43 for methadone and 0.50–2.00 for buprenorphine and norbuprenorphine
- Safety measures: Adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations were recorded throughout the study. Signs of withdrawal or toxicity were monitored

Results

Subject Disposition/Demographics

- 32 subjects were treated and completed the study
  - Median (range) age was 34.0 (24–55) years in Part 1 and 40.0 (26–63) years in Part 2
  - The majority of subjects were male: 11 (68.8%) in Part 1 and 12 (75.0%) in Part 2
  - The majority of subjects were White: 14 (87.5%) in Part 1 and 12 (75.0%) in Part 2

Safety

- There were no deaths, serious AEs, or AEs leading to discontinuation of study therapy
- There were no trends in emergent laboratory abnormalities and no AEs related to ECG abnormalities

Pharmacodynamics

- There were no clinically relevant trends in the changes from baseline of the overall scores for the COWS, SOWS, OOWS, or OOA. Scores following coadministration of FTR 600 mg ER BID were generally similar to those when methadone (in Part 1) or buprenorphine/naloxone (in Part 2) were administered alone

Pharmacokinetics

- Coadministration of methadone with FTR 600 mg ER BID did not have a meaningful impact on R-methadone, S-methadone, or total methadone PK relative to administration of methadone alone (**Figure 2a,b,c; Table 1**)
- Coadministration of buprenorphine/naloxone with FTR 600 mg ER BID increased buprenorphine and norbuprenorphine Cmax, AUC(0-tau), and C24 by 24%–39% (**Figure 2d,e; Table 2**)
- Geometric mean (%CV) TMR Cmax, AUC(0-tau), and C12 were 1498 (41) ng/mL, 9758 (40) ng*h/mL, and 409 (60) ng/mL, respectively, when FTR 600 mg ER BID was coadministered with methadone and 2052 (39) ng/mL, 13176 (35) ng*h/mL, and 468 (80) ng/mL, respectively, when FTR 600 mg ER BID was coadministered with buprenorphine/naloxone. TMR exposures were generally consistent with historical data[5]

Figure 2. Mean (+SD) Dose-Normalized Plasma Concentration-Time Profiles for R-Methadone (A), S-Methadone (B), Total Methadone (C), Buprenorphine (D), and Norbuprenorphine (E) With and Without FTR

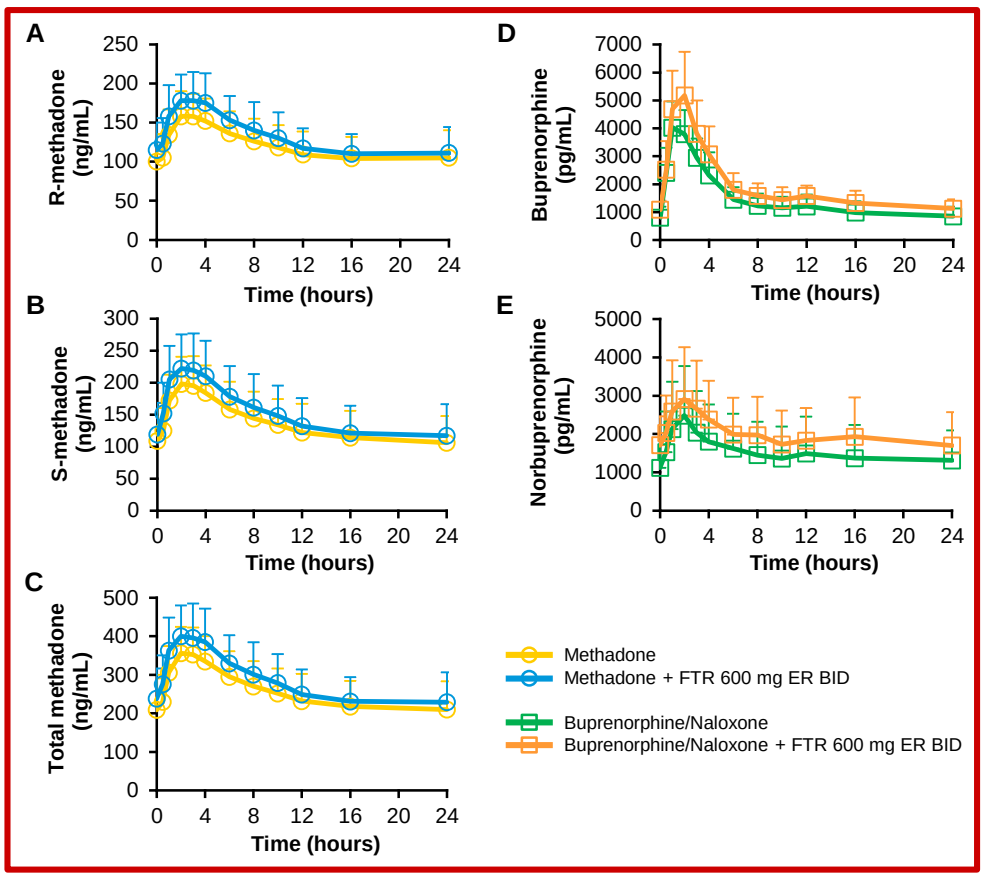


Table 1. Effect of FTR 600 mg ER BID on Dose-Normalized Methadone PK

		Adjusted Geometric Mean		GMR (90% CI)
Analyte	**Parameter**	**Treatment A**	**Treatment B**	**Treatment B vs A**
R-methadone	Cmax	162 (149, 176)	187 (173, 202)	1.15 (1.11, 1.20)
	AUC(0-tau)	2707 (2450, 2993)	3062 (2804, 3343)	1.13 (1.07, 1.19)
	C24	98.5 (86.3, 113)	107 (94.6, 121)	1.09 (1.01, 1.17)
S-methadone	Cmax	199 (180, 220)	228 (206, 252)	1.15 (1.10, 1.19)
	AUC(0-tau)	2967 (2593, 3396)	3412 (2974, 3915)	1.15 (1.09, 1.21)
	C24	97.3 (80.7, 117)	107 (87.8, 131)	1.10 (1.02, 1.19)
Total methadone	Cmax	362 (332, 395)	415 (382, 452)	1.15 (1.11, 1.19)
	AUC(0-tau)	5702 (5095, 6380)	6509 (5849, 7244)	1.14 (1.09, 1.20)
	C24	197 (170, 230)	216 (186, 252)	1.10 (1.02, 1.18)

Treatment A: methadone alone; Treatment B: methadone + FTR 600 mg ER BID. Cmax and C24 units = ng/mL; AUC(0-tau) units = ng*h/mL.

Table 2. Effect of FTR 600 mg ER BID on Dose-Normalized Buprenorphine PK

		Adjusted Geometric Mean		GMR (90% CI)
Analyte	**Parameter**	**Treatment C**	**Treatment D**	**Treatment D vs C**
Buprenorphine	Cmax	4187 (3835, 4572)	5206 (4534, 5977)	1.24 (1.06, 1.46)
	AUC(0-tau)	33867 (30230, 37942)	44090 (39652, 49024)	1.30 (1.17, 1.45)
	C24	780 (638, 953)	1082 (949, 1234)	1.39 (1.18, 1.63)
Norbupre-norphine	Cmax	2152 (1644, 2818)	2674 (2171, 3295)	1.24 (1.03, 1.51)
	AUC(0-tau)	30219 (22688, 40252)	41920 (33436, 52557)	1.39 (1.16, 1.67)
	C24	1104 (843, 1447)	1506 (1205, 1883)	1.36 (1.10, 1.69)

Treatment C: buprenorphine alone; Treatment D: buprenorphine/naloxone + FTR 600 mg ER BID. Cmax and C24 units = pg/mL; AUC(0-tau) units = pg*h/mL.

Conclusions

- Coadministration of FTR 600 mg ER BID with methadone did not have a meaningful impact on R-, S-, or total methadone exposures
  - Methadone may be coadministered with FTR 600 mg ER BID without dose adjustment
- Coadministration of FTR 600 mg BID with buprenorphine increased buprenorphine and norbuprenorphine exposures by 30% and 39%, respectively
  - Buprenorphine may be coadministered with FTR 600 mg ER BID without dose adjustment
  - The 90% CIs were contained within the protocol-defined boundaries for no clinically significant effect; however, consistent with other antiretrovirals with similar magnitudes of impact,[6,7] monitoring for clinical signs of sedation may be warranted
- Coadministration of FTR 600 mg ER BID with methadone or buprenorphine/naloxone was well tolerated and produced no new safety signals, including no clinically meaningful impact on trends of opiate withdrawal or overdose effects

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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 et al. *J Pharm Sci.* 2013;102:1742-1751. **2.** Langley et al. *Proteins.* 2015;83:331-350. **3.** Des Jarlais et al. *AIDS.* 2016;30:815-826. **4.** Kharasch. *Clin Pharmacol Drug Dev.* 2017;6:125-134. **5.** Vakkalagadda et al. ICAAC/ICC 2015; San Diego, CA. Poster 1676. **6.** Prezista® [package insert]. Janssen; 2017. **7.** Stribild® [package insert]. Gilead Sciences; 2017.