2500

Fostemsavir Drug-Drug Interaction Profile, an Attachment Inhibitor and Oral Prodrug of Temsavir, for Heavily Treatment-Experienced HIV-1 Infected Patients

Katy Moore,[1] A. Savannah Mageau,[2] Mindy Magee,[3] Pete Gorycki,[4] Peter Ackerman,[5] Cyril Llamoso[5]

[1]Clinical Pharmacology, ViiV Healthcare, Research Triangle Park, NC, USA; [2]PharmD Candidate, UNC Eshelman School of Pharmacy, Chapel Hill, NC, USA; [3]Clinical Pharmacology Modeling Simulation, GlaxoSmithKline, Upper Providence, PA, USA; [4]Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Upper Providence, PA, USA; [5]Clinical Development, ViiV Healthcare, Branford, CT, USA

Katy Moore, RPh, PharmD
5 Moore Drive
Research Triangle Park, NC 27709
katy.p.moore@viivhealthcare.com

Introduction

- Fostemsavir (FTR) is a first-in-class attachment inhibitor that is currently under investigation in Phase III trial in combination with other antiretroviral (ARV) agents in heavily treatment-experienced (HTE; multi-drug resistance) human immunodeficiency virus-1 (HIV-1) infected patients.
- FTR is an oral prodrug of temsavir (TMR), that specifically binds to the viral envelope protein glycoprotein 120 (gp120) near the CD4 receptor site and blocks attachment of the virus to the CD4 receptor on T-cells and other host immune cells.
- TMR is predominately metabolized by an esterase-mediated hydrolysis pathway (36.1%) with contributions from cytochrome P450 (CYP) 3A4-mediated oxidative pathway (21.2%).
- TMR is a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, and TMR and/or its metabolites inhibit BCRP and organic anion transporter protein 1B1/3 (OATP1B1/3).
- TMR does not inhibit or induce major CYP or uridine diphosphate glucuronosyltransferase (UGT) enzymes, and thus has minimal potential to cause CYP- or UGT-mediated drug-drug interactions (DDIs).
- FTR 600 mg BID with or without pharmacoenhancers will not have a clinically relevant impact on QTc prolongation.[1] Mean TMR Cmax following FTR 600 mg twice daily is 1770 ng/mL based on population pharmacokinetic analyses in HIV-1–infected, heavily treatment-experienced adult subjects and is approximately 4.2-fold lower than the TMR concentration associated with a clinically important increase in QTcF interval of 10 msec.

Objective

- To summarize FTR DDI profile to inform co-administration with other ARVs and drugs of various therapeutic classes typically utilized in HIV-1 infected patients based on the TMR absorption and metabolism/transporter profile.

Methods

- DDI data from 11 studies were utilized to inform the use of FTR with medications commonly administered to persons living with HIV; the impact of 17 drugs or drug combinations on TMR PK and the impact of TMR on the PK of 15 drugs were summarized and applied to other drugs with common underlying mechanisms.
- Clinically relevant DDIs were based on exposure-response (E-R) relationships.
- For FTR, the E-R relationships balanced the potential for Cmax-related QTc interval prolongation while optimizing Ctau exposures for antiviral effect. The safety and efficacy of FTR 600 mg BID was established in HIV-infected HTE subjects in the Phase III BRIGHTE Study receiving FTR and optimized background therapy.[2]

Results

Table 1. Summary of Effect of Co-administered Drugs on PK of TMR

Co-administered Drug(s) and Dose(s)		N	Geometric Mean Ratio (GMR) (90% CI) of TMR PK Parameters with/without Co-administered Drugs No Effect = 1.00		
			Cmax	AUC	Cτ
Co-administration with Antiretrovirals with and without PK Enhancers					
Atazanavir/ Ritonavir[3]	300 mg once daily/ 100 mg once daily	36	1.68 (1.58, 1.79)	1.54 (1.44, 1.65)	1.57 (1.28, 1.91)
Darunavir/ Cobicistat[4]	800 mg once daily/ 150 mg once daily	15	1.79 (1.62, 1.98)	1.97 (1.78, 2.18)	2.24 (1.75, 2.88)
Darunavir/ Ritonavir[5]	600 mg twice daily/ 100 mg twice daily	14	1.52 (1.28, 1.82)	1.63 (1.42, 1.88)	1.88 (1.09, 3.22)
Darunavir/ Ritonavir/ Etravirine[5]	600 mg twice daily/ 100 mg twice daily/ 200 mg twice daily	18	1.53 (1.32, 1.77)	1.34 (1.17, 1.53)	1.33 (0.98, 1.81)
Etravirine[5]	200 mg twice daily	14	0.52 (0.45, 0.59)	0.50 (0.44, 0.57)	0.48 (0.32, 0.72)
Raltegravir/ Tenofovir disoproxil fumarate[a,6]	400 mg twice daily/ 300 mg once daily	17	1.23 (0.92, 1.64)	1.07 (0.84, 1.34)	1.17 (0.59, 2.32)
Tenofovir disoproxil fumarate[7]	300 mg once daily	18	0.99 (0.86, 1.13)	1.00 (0.91, 1.11)	1.13 (0.77, 1.66)
Maraviroc[8]	300 mg twice daily	14	1.13 (0.96, 1.32)	1.10 (0.99, 1.23)	0.90 (0.69, 1.17)
Co-administration with PK Enhancers					
Ritonavir[3]	100 mg once daily	18	1.53 (1.31, 1.79)	1.45 (1.29, 1.61)	1.44 (1.00, 2.08)
Cobicistat[4]	150 mg once daily	16	1.71 (1.54, 1.90)	1.93 (1.75, 2.12)	2.36 (2.03, 2.75)
Co-administration with Rifamycins					
Rifabutin/ Ritonavir[9]	150 mg once daily/ 100 mg once daily	23	1.50 (1.38, 1.64)	1.66 (1.52, 1.81)	2.58 (1.95, 3.42)
Rifabutin[9]	300 mg once daily	22	0.73 (0.65, 0.83)	0.70 (0.64, 0.76)	0.59 (0.46, 0.77)
Rifampin[b,10]	600 mg once daily	15	0.24 (0.21, 0.28)	0.18 (0.16, 0.2)	NA
Co-administration with Other Drugs					
Famotidine[c,11]	40 mg single dose	24	1.01 (0.85, 1.21)	1.04 (0.87, 1.25)	0.90 (0.64, 1.28)

FTR dose 600 mg twice daily
[a]FTR dose 1200 mg daily (3 other FTR doses were examined with similar results). [b]FTR dose 1200 mg single dose. [c]FTR dose 600 mg single dose.

Table 2. Summary of Effect of TMR on PK of Co-administered Drugs

Co-administered Drug(s) and Dose(s)		N	GMR (90% CI) of PK Parameters of Co-administered Drugs with/without FTR No Effect = 1.00		
			Cmax	AUC	Cτ
Co-administration with Antiretrovirals					
Atazanavir/ Ritonavir[3]	300 mg once daily/ 100 mg once daily	18	1.03 (0.96, 1.10) 1.02 (0.96, 1.09)	1.09 (1.03, 1.15) 1.07 (1.03, 1.10)	1.19 (1.10, 1.30) 1.22 (1.12, 1.32)
Darunavir/ Ritonavir	600 mg twice daily/ 100 mg twice daily	13	0.98 (0.93, 1.04) 1.00 (0.86, 1.16)	0.94 (0.89, 1.00) 1.15 (0.99, 1.33)	0.95 (0.87, 1.04) 1.19 (1.06, 1.35)
Darunavir/ Ritonavir/ Etravirine	600 mg twice daily/ 100 mg twice daily/ 200 mg twice daily	13	0.95 (0.90, 1.01) 1.14 (0.96, 1.35) 1.18 (1.10, 1.27)	0.94 (0.89, 0.99) 1.09 (0.98, 1.22) 1.28 (1.20, 1.36)	0.88 (0.77, 1.01) 1.07 (0.97, 1.17) 1.28 (1.18, 1.39)
Etravirine	200 mg twice daily	14	1.11 (1.04, 1.19)	1.11 (1.05, 1.17)	1.14 (1.08, 1.21)
Tenofovir disoproxil fumarate[7]	300 mg once daily	18	1.18 (1.12, 1.25)	1.19 (1.12, 1.25)	1.28 (1.20, 1.38)
Maraviroc[8]	300 mg twice daily	13	1.01 (0.84, 1.20)	1.25 (1.08, 1.44)	1.37 (1.26, 1.48)
Raltegravir (RAL) PK following co-administration of RAL 400 mg twice daily + tenofovir disoproxil fumarate 300 mg once daily with FTR once or twice daily dosage regimens were within the range of historical data for RAL 400 mg twice daily alone.[6]					
Co-administration with Non-Antiretrovirals					
Rosuvastatin[12]	10 mg single dose	18	1.78 (1.52, 2.09)	1.69 (1.44, 1.99)	NA
Ethinyl estradiol/ Norethindrone[13]	0.030 mg once daily/ 1.5 mg once daily	26	1.39 (1.28, 1.51) 1.08 (1.01, 1.16)	1.40 (1.29, 1.51) 1.08 (1.03, 1.14)	NA NA
R(-) Methadone S(+) Methadone Total Methadone[14]	40 to 120 mg once daily	16	1.15 (1.11, 1.20) 1.15 (1.10, 1.19) 1.15 (1.11, 1.19)	1.13 (1.07, 1.19) 1.15 (1.09, 1.21) 1.14 (1.09, 1.20)	1.09 (1.01, 1.17) 1.10 (1.02, 1.19) 1.10 (1.02, 1.18)
Buprenorphine Norbuprenorphine[14]	8/2 to 24/6 mg once daily	16	1.24 (1.06, 1.46) 1.24 (1.03, 1.51)	1.30 (1.17, 1.45) 1.39 (1.16, 1.67)	1.39 (1.18, 1.63) 1.36 (1.10, 1.69)

FTR dose 600 mg twice daily

Discussion

- **Contraindications:**
  - Strong CYP3A inducers (e.g., rifampin) – TMR is partly metabolized by CYP3A4; strong CYP3A inducers significantly reduce TMR plasma concentrations, and may result in loss of virologic response.
  - Elbasvir/Grazoprevir (EBR/GZR) – TMR inhibits OATP1B1/3; although co-administration not studied, may result in clinically relevant increased plasma GZR concentrations which may increase the risk of ALT elevations.
- **Dose Modifications and Precautions:**
  - Estrogen-based therapies (e.g., oral contraceptives) – Plasma ethinyl estradiol (EE) Cmax and AUC increased ~40%; EE dose should be ≤30 µg and caution advised for patients with additional risk factors for thromboembolic events.
  - Statins – TMR inhibits OATP1B1/3 and BCRP, affecting the PK of certain statins that are substrates to these transporters. Use lowest possible starting statin dose, monitor for AEs (e.g., myopathy), and limit daily doses of certain statins (e.g., rosuvastatin ≤20 mg). For pravastatin, no clinically relevant interaction is expected.
  - Drugs known to prolong QT interval – FTR should be used with caution when co-administered with a drug with a known risk for Torsade de Pointes or in older patients or those with relevant pre-existing cardiac disease.
- **No Dose Adjustment:**
  - Drugs that increase gastric pH (e.g., famotidine) – TMR absorption not altered with increased gastric pH.
  - Strong CYP3A inhibitors (e.g., ritonavir, cobicistat) – Increased plasma TMR Cτ values observed from strong CYP3A inhibition do not result in clinically relevant changes in virologic response and are not above the threshold defined by the Cp-ddQTc analysis.[15]
  - Moderate CYP3A inducers (e.g., rifabutin, etravirine) – Decreased plasma TMR Cτ values do not result in clinically relevant changes in virologic response.
  - ARVs – No significant interactions are expected with co-administration across all currently available ARV classes (PI, NRTI, NNRTI, INI, CCR5 antagonist, and Entry inhibitor, including ibalizumab).
  - Opioid dependence therapy (methadone and buprenorphine) – No clinically relevant drug interactions were observed.

Conclusion

- FTR has a favorable DDI profile, therefore can be co-administered with other ARVs and most common treatments used to manage HIV co-infections or comorbidities without need for dose adjustment including strong CYP3A4 inhibitors. Dose adjustment is recommended for most statins and EE-based hormonal therapies. Strong CYP3A4 inducers (e.g., rifampin) are contraindicated.

Acknowledgments: We thank all study participants and their families and the study investigators. ViiV Healthcare acquired fostemsavir from Bristol-Myers Squibb and is the sponsor. We thank all Bristol-Myers Squibb scientists for their contributions. Editorial assistance was provided by MedThink, funded by ViiV Healthcare.

References: 1. Lagishetty C, et al. ASCPT. 2019: Poster 71. **2.** Quercia R, et al. IWHIVW. 2019: Poster 22. **3.** Zhu L, et al. AAC. 2015;59:3816-3822. **4.** Vakkalagadda B, et al. ICCAC. 2015: Abstract 1676. **5.** Savant Landry I, et al. CROI. 2015: Abstract 523. **6.** Landry I, et al. IWCP-HIV. 2015: Abstract 67. **7.** Zhu L, et al. IWCP-HIV. 2012: Abstract P_13. **8.** Chang M, et al. IWCPHHT. Abstract P_51. **9.** Adamczyk R, et al. CROI. 2015: Poster TUPEB277. **10.** Hruska M, et al. IWCPHIV. 2013: Abstract P_05. **11.** Magee M, et al. IWCPAT. 2017: Abstract P_37. **12.** Landry I, et al. CROI. 2016: Abstract 460. **13.** Magee M, et al. IAS. 2017: Abstract MOPEB0339. **14.** Sevinsky H, et al. IAS. 2017: Abstract MOPEB0338. **15.** Magee M, et al. IWCPAT. 2019: Abstract 25.