DRUG INTERACTIONS WITH ONCE-DAILY B/F/TAF IN COMBINATION WITH ONCE-WEEKLY RIFAPENTINE

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Disclosure: Presenting author Priyanka Arora is an employee of Gilead Sciences, Inc and holds stock in the company
Introduction and Objective

♦ Bictegravir, emtricitabine, tenofovir alafenamide (B/F/TAF) is a guidelines-recommended first-line, single-tablet once daily treatment for PWH¹-³

♦ Among people with LTBI, PWH are ~20 times more likely to develop active TB compared to people without HIV⁴
  – Standard of care includes cotreatment of LTBI and HIV concomitantly
  – Guidelines-recommended LTBI treatments include once weekly rifapentine (RPT) + isoniazid

♦ BIC is metabolized by UGT1A1 and CYP3A

♦ TAF is a substrate of P-gp, BCRP and OATP

♦ RPT is a strong inducer of CYP3A but with induction potency less than that of rifampin, its inductive effect on P-gp is currently unknown

♦ Objectives:
  – Evaluate the effect of once-weekly RPT administration on B/F/TAF and TFV (TAF major metabolite) plasma PK and TFV-DP (TAF/TFV active metabolite) PK in PBMCs
  – Assess the safety and tolerability of multiple-dose B/F/TAF administered with once weekly RPT

B, BIC, bictegravir; BCRP, breast cancer resistance protein; CYP3A, cytochrome P450 3A; F, FTC, emtricitabine; LTBI, latent TB infection; OATP, organic anion-transporting polypeptide; PBMC, peripheral blood mononuclear cells; P-gp, p-glycoprotein; PWH, people living with HIV; RPT, rifapentine; TAF, tenofovir alafenamide; TB, tuberculosis; TFV, tenofovir; TFV-DP, TFV-diphosphate; UGT1A1, uridine diphospho-glucuronosyltransferase family 1A1.

A Phase 1, open-label, 3-period fixed sequence, multiple-dose, single-center study was conducted in 30 HIV-negative healthy volunteers.

An even distribution (1:1) of healthy male and nonpregnant, nonlactating female participants aged 18–45 y were enrolled in the study.

PK in plasma and PBMC was assessed at pre-specified timepoints.

PK parameters were estimated by noncompartmental methods using WinNonlin v8.2.

Statistical analysis:
- GLSM ratios and corresponding 90% CIs were used for statistical comparisons of exposures
- Test: B/F/TAF qd coadministered with RPT qwk or administered 12 h after RPT; reference: B/F/TAF qd alone

*Certara USA, Inc., Princeton, NJ. CI, confidence intervals; GLSM, geometric least-squares mean; qd, once daily; qwk, once weekly.
Results: BIC PK

BIC Plasma PK Following B/F/TAF qd Alone vs Coadministered With or Administered 12-h After RPT qwk

PK Parameter Mean (%CV) | B/F/TAF qd n=29 | B/F/TAF qd + RPT qwk codosed n=29 | B/F/TAF qd + RPT qwk 12-h stagger n=28 | %GLSM (90% CI) | Codosed vs alone | 12-h stagger vs alone
--- | --- | --- | --- | --- | --- | ---
C\(_{\text{max}}\), ng/mL | 6870 (16.3) | 6880 (16.9) | 6590 (16.6) | 100 (95.5, 105) | 96.0 (91.8, 100) |
AUC\(_{\text{tau}}\), h·ng/mL | 96100 (23.3) | 81400 (17.9) | 70800 (18.3) | 85.5 (81.3, 89.8) | 74.1 (70.2, 78.3) |
C\(_{\text{tau}}\), ng/mL | 2510 (28.1) | 1520 (26.6) | 1080 (27.2) | 60.4 (56.3, 64.7)* | 42.5 (39.1, 46.2)* |
Median T\(_1/2\), h (Q1, Q3) | 20.7 (18.5, 22.3) | 10.3 (9.71, 11.2) | 8.82 (8.07, 9.23) |

*Outside no-effect drug-drug interaction boundaries; †Relative to date of first study drug administration (Day 1). AUC\(_{\text{tau}}\), area under plasma concentration-time curve over dosing interval; C\(_{\text{max}}\), maximal concentration; C\(_{\text{tau}}\), trough concentration; CV, coefficient of variation; paEC\(_{95}\), protein-adjusted 95% effective concentration; SD, standard deviation.

Key findings:
- BIC C\(_{\text{tau}}\) reduced by as low as 83% by Day 4 post RPT dosing (nadir)
- BIC C\(_{\text{tau}}\) never recovered back to steady state concentrations between RPT doses
- 12-hr staggered (vs coadministration) of RPT qwk resulted in more pronounced decline in BIC C\(_{\text{tau}}\)

Geometric Mean BIC C\(_{\text{tau}}\), ng/mL (SD)
Results: PK of Other Analytes

Summary of PK Parameter Estimates Across Study Treatments

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♦ Coadministration of RPT qwk did not significantly affect the PK of FTC, TAF, TFV or TFV-DP

Circles and bars indicate % GLSM ratio and 90% CIs, respectively. Shaded area indicates default no-effect boundary of 70–143%.
Conclusions

♦ All study treatments were safe and well tolerated

♦ BIC $C_{tau}$ was ~35–83% lower following administration of B/F/TAF qd + RPT qwk, indicating a significant impact of RPT on BIC PK due to potent induction of CYP3A4

♦ After accounting for ~83% reduction in BIC $C_{tau}$ at the nadir, trough levels are predicted to fall below the paEC$_{95}$ (inhibitory quotient of 1) in some patients if daily B/F/TAF is administered with weekly RPT

♦ No clinically significant changes in the PK of FTC, TAF, TFV, and TFV-DP were observed with coadministration of weekly RPT

♦ Based on the substantial reduction in BIC $C_{tau}$, use of single tablet regimen B/F/TAF with weekly RPT is not recommended

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We extend our thanks to the participants, their families and all participating study investigators and staff. This study was funded by Gilead Sciences, Inc.