No Clinically Relevant Effect of Patient Demographic or Disease Covariates on the Exposures of Bictegravir and Tenofovir Alafenamide Following Administration of a B/F/TAF Single-Tablet Regimen to HIV-1-Infected Patients

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Introduction

- Bictegravir (BIC)/emtricitabine/tenofovir alafenamide (B/F/TAF 50/200/25 mg) is a single tablet regimen (STR) approved in Australia, Canada, EU, and USA for treatment of HIV-1 infection in treatment-naive and virologically suppressed adults without resistance to its components1
- B/F/TAF is a Department of Health and Human Services and International Antiviral Society guidelines-recommended initial regimen for most HIV-1–infected patients2
- B/F/TAF requires qd dosing without regard to food, and has limited testing requirements prior to initiation and few known drug-drug interactions
- In five Phase 3 studies of HIV-1–infected patients, B/F/TAF was safe and efficacious, with no development of resistance3-5
- A population-based pharmacokinetic (PK) model was developed to understand the clinical covariates of the PK of BIC and TAF in HIV-1–infected patients when administered as B/F/TAF 50/200/25 mg qd

Objectives

- To determine the effects of demographic, pathophysiologic, and HIV-1–related covariates on the PK of BIC and TAF to better understand clinical factors that may affect exposure in individual patients

Methods

Population PK Modeling

- Population PK models for BIC and TAF were developed using pooled intensive and sparse plasma concentration data (8752 and 4201 observations, respectively) from 18 Phase 1 and 3 studies in healthy volunteers (HVs) and patients with HIV-1 infection (BIC: n=1318; TAF: n=1409)
- A nonlinear mixed-effects modeling approach using a 1st-order conditional estimation with interaction method in NONMEM® 7.3 (ICON plc, Dublin, Ireland) was employed

Covariate Effects

- Significance covariates were determined using a forward addition and backward elimination method (based on significance levels of p < 0.01 and p < 0.001, respectively)
- Demographics: baseline age, sex, race (white vs black or African-American vs Asian vs other), body weight (BW), and HIV-1 status (HVs vs HIV-1–infected patients)
- Pathophysiologic covariates: baseline creatinine clearance, prior treatment experience (naïve vs experienced), and concomitant administration of H2-receptor antagonists (H2RAs) or proton pump inhibitors (PPIs)
- Other covariates: fasting/fed status (never vs sometimes vs always fed) and baseline hepatitis B or C virus (HBV or HCV, respectively) coinfection status

- To examine the influence of patient covariates on the steady-state exposures of BIC (area under plasma concentration-time curve over dosing interval [AUC]) and TAF (Cmax, ng/mL) and concentration at end of dosing interval [C(last)] and TAF (AUC,ng/mL; Cmax, ng/mL):
  - Sensitivity analyses of significant covariates were performed
  - Exposures were stratified by covariate and compared

Results

- The developed population PK models adequately described BIC and TAF PK (data not shown)
  - BIC PK was described using a 1-compartment model, with 1st-order absorption, a lag time, and 1st-order elimination from the central compartment
    - Only HIV-1 status, BW, and baseline PPI status were identified as statistically significant covariates
  - TAF PK was described by a 2-compartment model with sequential 0- then 1st-order absorption, with 1st-order elimination from the central compartment and redistribution from the peripheral compartment
    - Only HIV-1 status and sex on clearance were identified as statistically significant covariates

- The sensitivity analysis showed that baseline BW was the greatest contributor to the variability of BIC exposure (34% for AUC across 90% of plausible range of BW)
- The contribution of HIV-1 status or baseline PPI use to the variability in BIC exposure was low (<5%)

Conclusions

- Considering the favorable B/F/TAF safety profile and high virologic response rates across the Phase 3 program,6 all demographic and disease covariates evaluated were determined to have no clinically relevant impact on BIC or TAF exposure in HIV-1–infected patients
- No dose adjustment of BIC or TAF is necessary for the evaluated patient demographic or disease covariates

References