Introduction

- Bictegravir (BIC; B), a novel, potent integrase strand transfer inhibitor (INSTI) with a high barrier to resistance, is coformulated with emtricitabine and tenofovir alafenamide into a single-tablet regimen (B/F/TAF), and is approved in Australia, Canada, Europe, and USA as Biktarvy® (Gilead)10
- Unboosted, low potential for drug-drug interactions, and once-daily dosing without regard to food
- B/F/TAF has shown noninferiority to Week 48 to current standard-of-care comparators, with no treatment-emergent resistance, and was well tolerated across 5 randomized, Phase 3 studies in adults living with HIV-111,112
  - BIC demonstrated a wide therapeutic window12
  - A mean BIC inhibitory quotient (IQ) of 16.1 was observed in the Phase 3 registral studies of B/F/TAF (N=584)
  - IQ is defined as trough plasma concentration (Cτ) divided by protein-adjusted effective concentration that inhibits 95% of wild-type HIV-1 virus (EC50)
- Like other INSTIs, adherence may be decreased on coadministration with polyvalent cation-containing (PVCC) antacids or supplements via chelation, resulting in decreased BIC exposures113

Objectives

Primary:
- To evaluate the effect of administration of aluminum/magnesium (Al/Mg) antacids and calcium (Ca) or iron (Fe) supplements with B/F/TAF fixed-dose combination (FDC) on BIC pharmacokinetics (PK)
  - Can this possible effect be mitigated by food?
  - Can this possible effect be mitigated by staggered administration?

Secondary:
- To evaluate the safety and tolerability of B/F/TAF when given alone or in combination with PVCC antacids/supplements
- To conservatively predict the impact of PVCC antacid supplement coadministration on BIC PK to assess the potential impact of coadministration on BIC pharmacodynamics (PD) in HIV-1-infected patients administered once-daily B/F/TAF FDC

Methods

Study Design

- Phase 1, open-label, single-dose, fixed-sequence, multiple-cohort, multiple-period study in healthy subjects
- 42 subjects (14/cohort) were enrolled
- All treatments were administered as single doses
- A moderate fat meal (600 calories) was administered among fed treatments

Reference treatment: B/F/TAF (50/200/25 mg) FDC, fasted

Test treatments:
- B/F/TAF+FDC + Al/Mg antacid (hydride 1600 mg) or fed (Cohort 3), simultaneous
- B/F/TAF FDC + Ca carbonate (1200 mg) supplement, fasted (Cohort 1) or fed (Cohort 3), simultaneous
- B/F/TAF+FDC + Fe fumarate (324 mg) supplement, fasted (test) or fed (reference)

PK Analyses

- Only BIC, and not F or TAF, plasma concentrations were determined
- BIC concentrations in plasma were analyzed using validated liquid chromatography–tandem mass spectrometry assays
- PK parameters were estimated using Phoenix® WinNonlin® 6.4
- PK parameters (mean ± coefficient of variation (CV%)) included area under curve from time 0 to τ (AUCτ), h·ng/mL and concentration 24 h postdose (C24, ng/mL)
- BIC exposures (AUC∞, maximum concentration [Cmax], and C24) from test treatments were compared with the reference treatment as geometric least-squares mean (GLSM) ratios and associated 90% confidence intervals (CI), which were estimated using analysis of variance
- The lack of drug-drug interaction boundary was 70%–143%

Prediction of BIC IQ in HIV-1–Infected Patients Coadministered Daily PVCC Antacids

- To predict BIC exposure in infected patients with daily use of PVCC antacids/supplements:
  - Mean BIC IQ from the B/F/TAF Phase 3 registral studies was modeled by the observed Cτ/GLSM ratio for each PVCC antacid/supplement regimen studied
  - Individual BIC IQ values in the B/F/TAF Phase 3 registral studies (treatment-naive HIV–1–infected patients) were predicted assuming all patients took their daily dose of B/F/TAF under fasted conditions 2 h after administering an Al/Mg antacid

Results

- Safety
  - All treatments were generally well tolerated; n=41/42 completed studies (treatment-naïve HIV-1‒infected patients) were predicted
  - During staggered coadministration of B/F/TAF 2 h before and 2 h after Al/Mg antacid simultaneous washout, a moderate decrease (79%) in BIC exposure was observed in the largest decrease (79%) in BIC exposure was observed in the

- Conclusions

- Decreased BIC exposure from chelation by PVCC antacids/supplements can be attenuated by staggering administration ± 2 h and administering with food
- Mean IQ of 7.6 is predicted in HIV-1–infected patients coadministering B/F/TAF in a fasted state 2 h after PVCC antacid/supplement therapy
  - Reduction in BIC exposure (IQ = 1) is unlikely
- PVCC antacids/supplements are not expected to reduce BIC efficacy
- High IQ values and associated efficacy of BIC in the B/F/TAF registral trials suggests its flexible use in patients coadministering PVCC antacids/supplements either simultaneously fed or fasted when staggered ± 2 h

- Administration of food attenuated the chelating effect of PVCC antacids/supplements
  - BIC C24 was modestly reduced (%CV) with Al/Mg antacid
  - Ca supplement (test)
- The effects on BIC PK and IQ were limited when PVCC antacids/supplements were administered either simultaneously with B/F/TAF under fed conditions or staggered from B/F/TAF administration by ± 2 h under fasted conditions
  - Both coadministration conditions are expected to yield BIC values within the therapeutic window for HIV-1–infected patients, as previously defined

- Predicted IQ After Daily Al/Mg Antacid Coadministration in HIV–1–Infected Patients**

<table>
<thead>
<tr>
<th>Condition</th>
<th>C24, μg/mL</th>
<th>n</th>
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<tbody>
<tr>
<td>Fed</td>
<td>1.22 (43.9)</td>
<td>13</td>
</tr>
<tr>
<td>Ca + B/F/TAF</td>
<td>21.9 (17.8, 27.0)</td>
<td>13</td>
</tr>
<tr>
<td>Al/Mg + B/F/TAF</td>
<td>11.23 (14.1, 18.6)</td>
<td>13</td>
</tr>
<tr>
<td>Alone, B/F/TAF administered fasted alone; Ca, fed, B/F/TAF administered fasted with Ca supplement; Fe, B/F/TAF administered fasted with Fe supplement.</td>
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- Comparisons with B/F/TAF alone, BIC C24 was substantially reduced following simultaneous fasted administration of B/F/TAF with Al/Mg antacids (%GLSM 22%) or Fe supplements (%GLSM 37%)
  - Simultaneous fasted coadministration of B/F/TAF with Al/Mg- or Fe-containing antacids/supplements is not recommended
  - The effects on BIC PK and IQ were limited when PVCC antacids/supplements were administered either simultaneously with B/F/TAF under fed conditions or staggered from B/F/TAF administration by ± 2 h under fasted conditions
  - Both coadministration conditions are expected to yield BIC values within the therapeutic window for HIV–1–infected patients, as previously defined

- The analysis revealed that if all patients in the Phase 3 registral studies were administered B/F/TAF 2 h after Al/Mg antacid, mean BIC IQ (CV%) is predicted to be 7.6 (44%)