P260

Pharmacokinetics of Bictegravir in Combination With Polyvalent Cation-Containing Antacids and Supplements

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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)[1-4]
  - Unboosted, low potential for drug-drug interactions, and once-daily dosing without regard to food
- B/F/TAF has shown noninferiority at 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-1[5-9]
  - B/F/TAF continued to be noninferior to dolutegravir/abacavir/lamivudine at Week 96 in an ongoing study[10]
  - BIC demonstrated a wide therapeutic window[11]
- A mean BIC inhibitory quotient (IQ) of 16.1 was observed in the Phase 3 registrational studies of B/F/TAF (N=584)
  - IQ is defined as trough plasma concentration (C_τ) divided by protein-adjusted effective concentration that inhibits 95% of wild-type HIV-1 virus activity (EC_{95})
- Like other INSTIs, absorption of BIC may be decreased on coadministration with polyvalent cation-containing (PVCC) antacids or supplements via chelation, resulting in decreased BIC exposures[12-15]

Objectives

Primary:

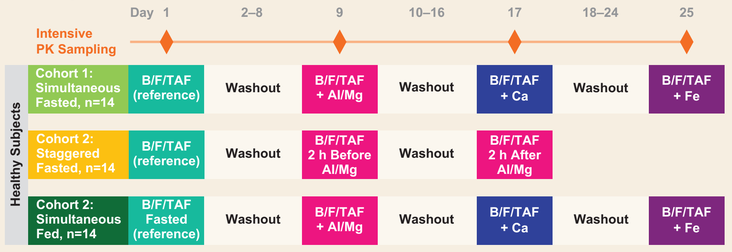
- To evaluate the effect of administration of aluminum/magnesium (Al/Mg) antacids and calcium (Ca) or iron (Fe) supplements with B/F/TAF fixed-dose combination (FDC) on BIC pharmacokinetics (PK)
  - Can this possible effect be mitigated by food?
  - Can this possible effect be mitigated by staggered 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 during fed treatments
- **Reference treatment:** B/F/TAF (50/200/25 mg) FDC, fasted
- **Test treatments:**
  - B/F/TAF FDC + Al/Mg antacids (Al hydroxide 1600 mg/Mg hydroxide 1600 mg/simethicone 160 mg), fasted (Cohort 1) or fed (Cohort 3), simultaneous
  - B/F/TAF FDC staggered 2 h before or after Al/Mg antacid, fasted (Cohort 2)
  - 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 (Cohort 1) or fed (Cohort 3), simultaneous

PK Analyses

- Only BIC, and not F nor 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 (Certara, LP, Princeton, New Jersey, USA)
- PK parameters (mean [% coefficient of variation (CV)]) included area under curve from time 0 to ∞ (AUC_∞, h·ng/mL) and concentration 24 h postdose (C_{24}, ng/mL)
- BIC exposures (AUC_∞, maximum concentration [C_{max}], and C_{24}) 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 HIV-1–infected patients with daily use of PVCC antacids/supplements:
  - Mean BIC IQ from the B/F/TAF Phase 3 registrational studies was multiplied by the observed C_{24} GLSM ratio for each PVCC antacid/supplement regimen studied
  - Individual BIC IQ values in the B/F/TAF Phase 3 registrational studies (treatment-naïve 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

Baseline Characteristics

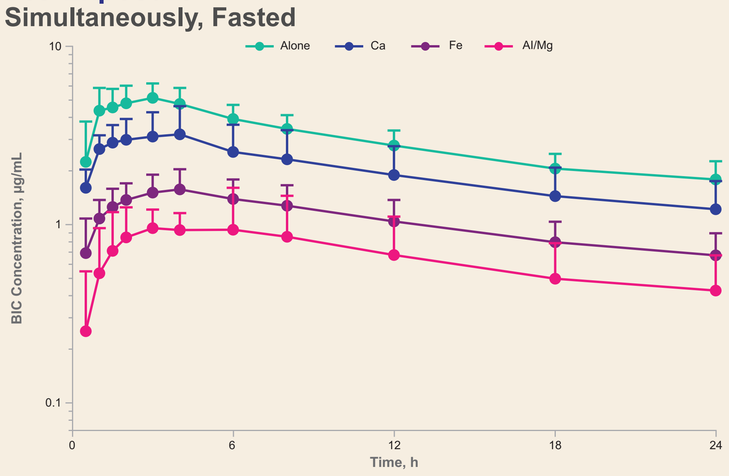
	Cohort 1 Fasted, Simultaneous n=14	Cohort 2 Fasted, Staggered n=14	Cohort 3 Fed, Simultaneous n=14
Median age, y (range)	32 (25–41)	29 (22–43)	41 (27–45)
Female, %	29	29	36
Median BMI, kg/m² (range)	26 (22–30)	26 (22–29)	28 (25–30)
Median $eGFR_{CG}$, mL/min (range)	119 (98–168)	129 (98–152)	117 (91–161)
Race/ethnicity, %			
Black/African-American	43	14	29
White	57	86	71
Hispanic/Latino	57	86	64

BMI, body mass index; $eGFR_{CG}$, estimated glomerular filtration rate (Cockcroft-Gault).

Safety

- All treatments were generally well tolerated; n=41/42 completed the study
  - 1 subject in Cohort 2 discontinued due to treatment-related Grade 2 urticaria
  - No other Grade ≥2 adverse events or laboratory abnormalities occurred

Effects of PVCC Antacids and Supplements on BIC Exposure
Simultaneously, Fasted

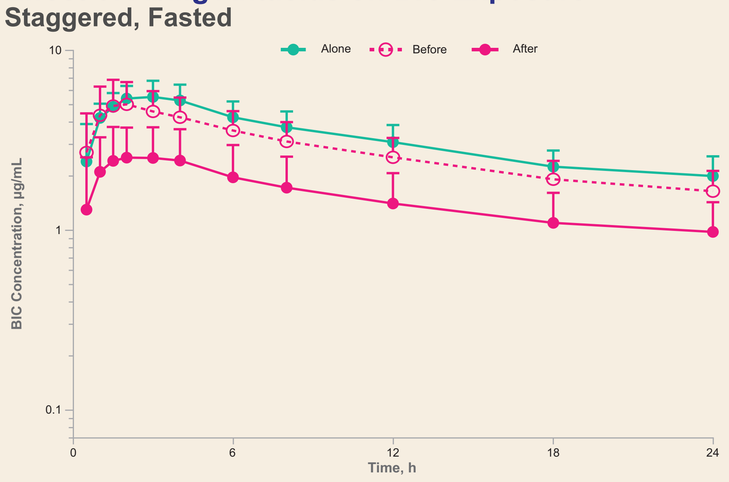


	BIC PK Parameter, Mean (%CV)	Test n=14	B/F/TAF Alone, Fasted (reference) n=14	% GLSM Ratio (90% CI)
B/F/TAF fasted + Al/Mg antacid (test)	AUC_∞, h·µg/mL	28.0 (52.5)	122 (24.4)	21.2 (17.6, 25.7)
	C_{max}, µg/mL	1.20 (52.0)	5.64 (18.8)	19.9 (16.5, 24.0)
	C_{24}, µg/mL	0.427 (57.4)	1.80 (26.3)	21.9 (17.8, 27.0)
B/F/TAF fasted + Ca supplement (test)	AUC_∞, h·µg/mL	85.0 (43.1)	122 (24.4)	66.7 (56.7, 78.4)
	C_{max}, µg/mL	3.44 (36.9)	5.64 (18.8)	58.3 (50.7, 67.0)
	C_{24}, µg/mL	1.22 (43.9)	1.80 (26.3)	64.9 (54.5, 77.3)
B/F/TAF fasted + Fe supplement (test)	AUC_∞, h·µg/mL	46.1 (32.9)	122 (24.4)	37.1 (33.0, 41.8)
	C_{max}, µg/mL	1.67 (27.1)	5.64 (18.8)	29.1 (25.9, 32.7)
	C_{24}, µg/mL	0.675 (32.8)	1.80 (26.3)	36.9 (32.6, 41.8)

Al/Mg, B/F/TAF administered fasted with Al/Mg antacid; Alone, B/F/TAF administered fasted alone; Ca, B/F/TAF administered fasted with Ca supplement; Fe, B/F/TAF administered fasted with Fe supplement.

- PVCC antacids/supplements coadministered simultaneously with B/F/TAF under fasted conditions reduced BIC AUC_∞; the largest decrease (79%) in BIC exposure was observed in the presence of Al/Mg antacids
- Ca and Fe supplements had less effect on BIC absorption than Al/Mg antacids

Effect of Al/Mg Antacids on BIC Exposure
Staggered, Fasted

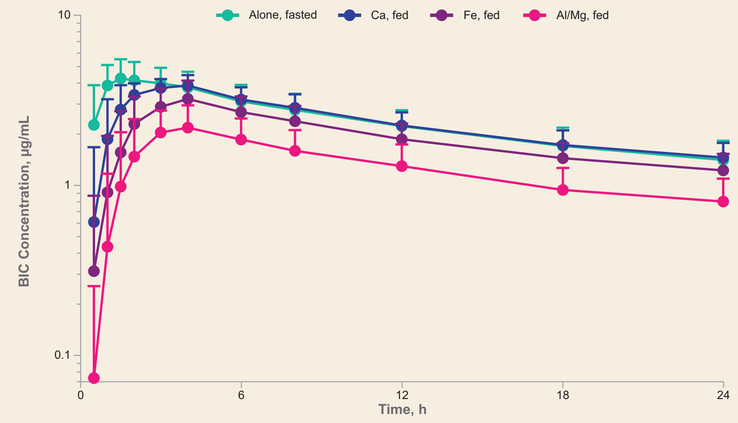


	BIC PK Parameter, Mean (%CV)	Test n=13	B/F/TAF Alone, Fasted (reference) n=14	% GLSM Ratio (90% CI)
B/F/TAF fasted 2h before Al/Mg antacid (test)	AUC_∞, h·µg/mL	116 (30.3)	133 (27.0)	86.7 (81.0, 92.8)
	C_{max}, µg/mL	5.62 (22.7)	5.92 (16.5)	93.4 (87.5, 99.7)
	C_{24}, µg/mL	1.70 (27.9)	2.01 (28.3)	85.5 (80.0, 91.4)
B/F/TAF fasted 2h after Al/Mg antacid (test)	AUC_∞, h·µg/mL	67.7 (47.0)	133 (27.0)	47.7 (38.3, 59.4)
	C_{max}, µg/mL	2.74 (48.3)	5.92 (16.5)	41.5 (33.3, 51.8)
	C_{24}, µg/mL	0.986 (44.0)	2.01 (28.3)	46.6 (37.8, 57.6)

After, B/F/TAF administered fasted 2 h after Al/Mg antacid; Alone, B/F/TAF administered fasted alone; Before, B/F/TAF administered fasted 2 h before Al/Mg antacid.

- Separation of B/F/TAF dose by as little as 2 h attenuated the chelating effect of PVCC antacids/supplements
  - Staggering of B/F/TAF 2 h before and 2 h after Al/Mg antacid administration resulted in modest decreases in BIC AUC_∞ (23% and 52%, respectively)

Effects of PVCC Antacids and Supplements on BIC Exposure
Simultaneously, Fed

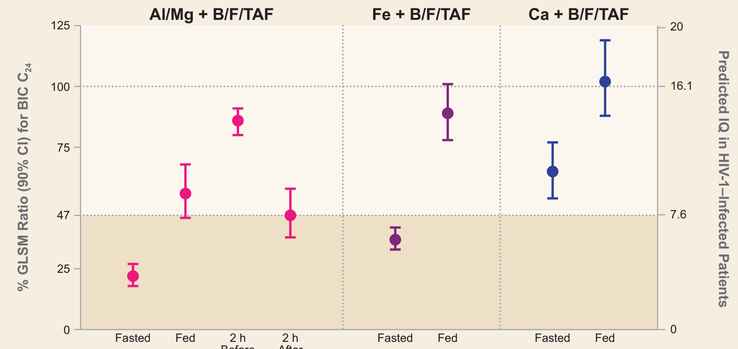


	BIC PK Parameter, Mean (%CV)	Test n=14	B/F/TAF Alone, Fasted (reference) n=14	% GLSM Ratio (90% CI)
B/F/TAF fed + Al/Mg antacid (test)	AUC_∞, h·µg/mL	50.8 (34.8)	93.7 (27.2)	53.3 (44.2, 64.1)
	C_{max}, µg/mL	2.45 (31.4)	4.70 (23.6)	51.5 (42.7, 62.0)
	C_{24}, µg/mL	0.804 (36.4)	1.41 (29.7)	56.0 (46.2, 67.9)
B/F/TAF fed + Ca supplement (test)*	AUC_∞, h·µg/mL	94.8 (21.2)	93.7 (27.2)	103 (89.0, 120)
	C_{max}, µg/mL	4.11 (13.7)	4.70 (23.6)	89.6 (77.8, 103)
	C_{24}, µg/mL	1.46 (22.1)	1.41 (29.7)	102 (88.1, 119)
B/F/TAF fed + Fe supplement (test)	AUC_∞, h·µg/mL	77.3 (24.8)	93.7 (27.2)	83.8 (74.1, 94. 9)
	C_{max}, µg/mL	3.49 (23.2)	4.70 (23.6)	75.1 (64.8, 87.1)
	C_{24}, µg/mL	1.23 (25.0)	1.41 (29.7)	88.9 (78.1, 101)

*n=13 for test treatment. Al/Mg, fed, B/F/TAF administered fed with Al/Mg antacid; Alone, fasted, B/F/TAF administered fasted alone; Ca, fed, B/F/TAF administered fed with Ca supplement; Fe, fed, B/F/TAF administered fed with Fe supplement.

- Administration of food attenuated the chelating effect of PVCC antacids/supplements
  - BIC AUC_∞ was modestly reduced (47%) with Al/Mg antacid
  - BIC AUC_∞ was unaffected by Ca and Fe supplements

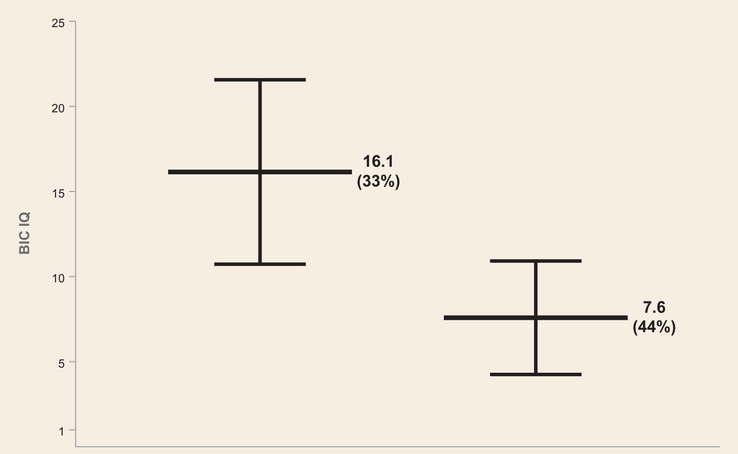
Summary of BIC C_{24} Changes After Various PVCC Antacid/Supplement Coadministration Conditions*



*IQ calculated via product of BIC AUC GLSM ratio and mean BIC IQ from B/F/TAF registrational trials (IQ 16.1); *beige and brown shaded areas* denote BIC IQ within and outside of, respectively, BIC therapeutic window, as previously defined.[11]

- Compared with B/F/TAF alone, BIC C_{24} 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 IQ values within the therapeutic window for HIV-1–infected patients, as previously defined[11]

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



*Mean IQ (%CV) in Phase 3 registrational studies was 16.1 (33%)[11]; BIC C_{24} GLSM ratio was 0.47 and test C_{24} %CV was 44% when B/F/TAF was administered fasted 2 h after Al/Mg antacid.

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

Conclusions

- Decreased BIC exposure from chelation by PVCC antacids/supplements can be attenuated by staggering administration ± 2 h and/or 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 registrational trials supports its flexible use in patients coadministering PVCC antacids/supplements either simultaneously fed or fasted when staggered ± 2 h

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