

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

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Introduction

- Bicitegravir (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-1⁵⁻⁹
 - B/F/TAF continued to be noninferior to dolutegravir/abacavir/lamivudine at Week 96 in an ongoing study¹⁰
 - BIC demonstrated a wide therapeutic window¹¹
- 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 (C₂₄) divided by protein-adjusted effective concentration that inhibits 95% of wild-type HIV-1 virus activity (EC₉₅)
- 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 exposures¹²⁻¹⁵

Objectives

Primary:

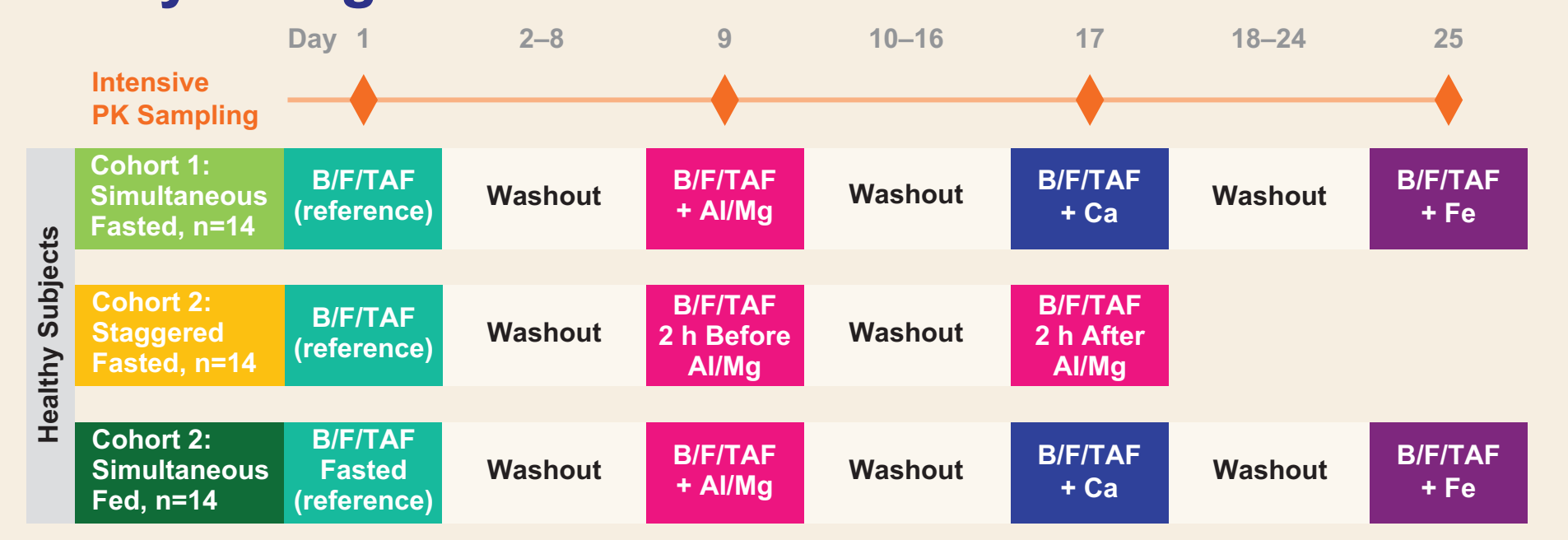
- To evaluate the effect of administration of aluminum/magnesium (Al/Mg) antacids and calcium (Ca) or iron (Fe) supplements with B/F/TAF fixed-dose combination (FDC) on BIC pharmacokinetics (PK)
 - Can this possible effect be mitigated by food?
 - Can this possible effect be mitigated by staggered administration?

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 (C₂₄, ng/mL)
- BIC exposures (AUC_∞, maximum concentration [C_{max}], 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 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 C₂₄ 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

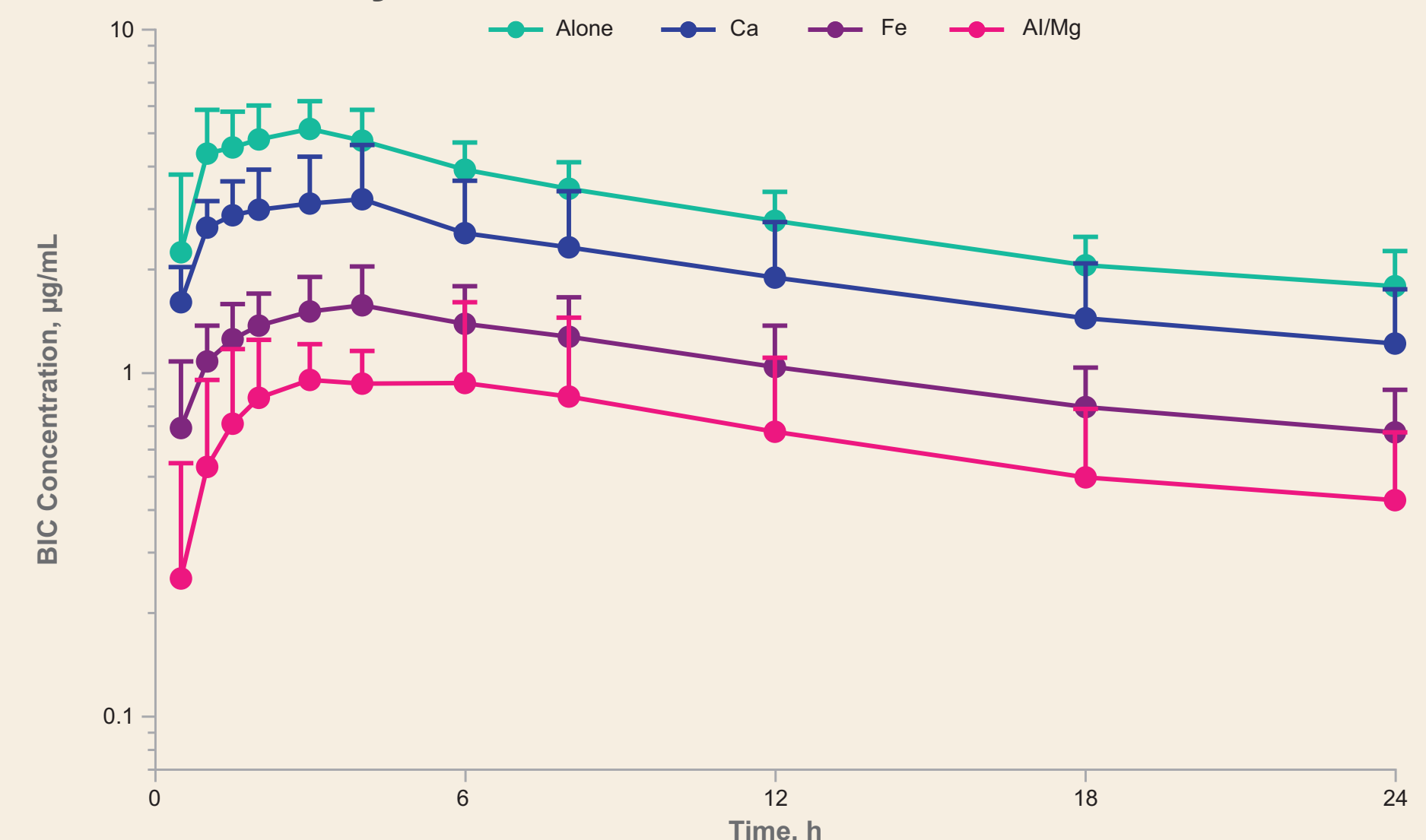
	Cohort 1 Fasted, Simultaneous n=14	Cohort 2 Fasted, Staggered n=14	Cohort 3 Fed, Simultaneous n=14
Median age, y (range)	32 (25–41)	29 (22–43)	41 (27–45)
Female, %	29	29	36
Median BMI, kg/m ² (range)	26 (22–30)	26 (22–29)	28 (25–30)
Median eGFR _{CRCL} , mL/min (range)	119 (98–168)	129 (98–152)	117 (91–161)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

BMI, body mass index; eGFR_{CRCL}, 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

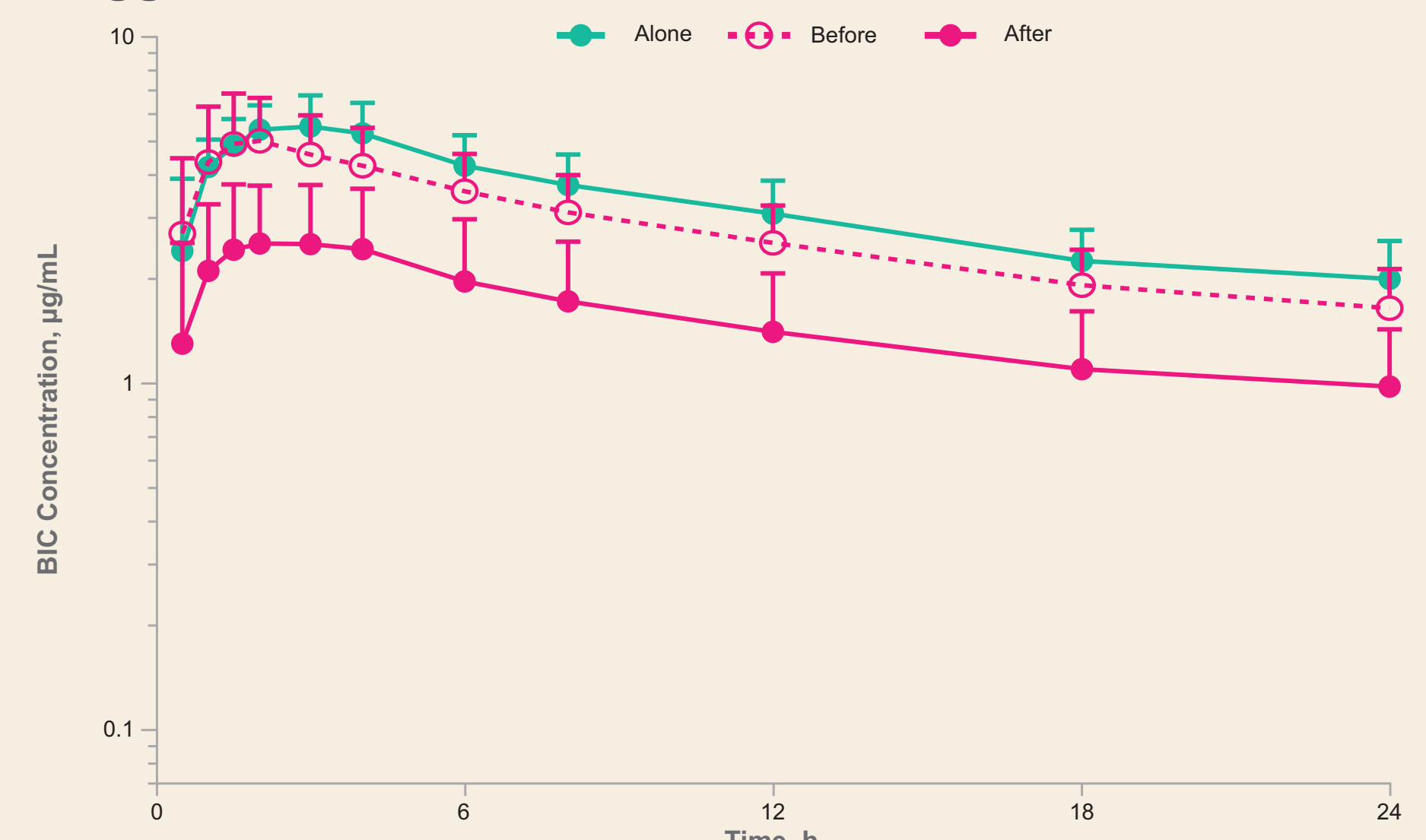


BIC PK Parameter, Mean (%CV)	Test n=14	B/F/TAF Alone, Fasted (reference) n=14	% GLSM Ratio (90% CI)
B/F/TAF fasted + Al/Mg antacid (test)	AUC _∞ , h·µg/mL: 28.0 (52.5) C _{max} , µg/mL: 1.20 (52.0) C ₂₄ , µg/mL: 0.427 (57.4)	122 (24.4) 5.64 (18.8) 1.80 (26.3)	21.2 (17.6, 25.7) 19.9 (16.5, 24.0) 21.9 (17.8, 27.0)
B/F/TAF fasted + Ca supplement (test)	AUC _∞ , h·µg/mL: 85.0 (43.1) C _{max} , µg/mL: 3.44 (36.9) C ₂₄ , µg/mL: 1.22 (43.9)	122 (24.4) 5.64 (18.8) 1.80 (26.3)	66.7 (56.7, 78.4) 58.3 (50.7, 67.0) 64.9 (54.5, 77.3)
B/F/TAF fasted + Fe supplement (test)	AUC _∞ , h·µg/mL: 46.1 (32.9) C _{max} , µg/mL: 1.67 (27.1) C ₂₄ , µg/mL: 0.675 (32.8)	122 (24.4) 5.64 (18.8) 1.80 (26.3)	37.1 (33.0, 41.8) 29.1 (25.9, 32.7) 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 2 h before Al/Mg antacid (test)	AUC _∞ , h·µg/mL: 116 (30.3) C _{max} , µg/mL: 5.62 (22.7) C ₂₄ , µg/mL: 1.70 (27.9)	133 (27.0) 5.92 (16.5) 2.01 (28.3)	86.7 (81.0, 92.8) 93.4 (87.5, 99.7) 85.5 (80.0, 91.4)
B/F/TAF fasted 2 h after Al/Mg antacid (test)	AUC _∞ , h·µg/mL: 67.7 (47.0) C _{max} , µg/mL: 2.74 (48.3) C ₂₄ , µg/mL: 0.986 (44.0)	133 (27.0) 5.92 (16.5) 2.01 (28.3)	47.7 (38.3, 59.4) 41.5 (33.3, 51.8) 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.

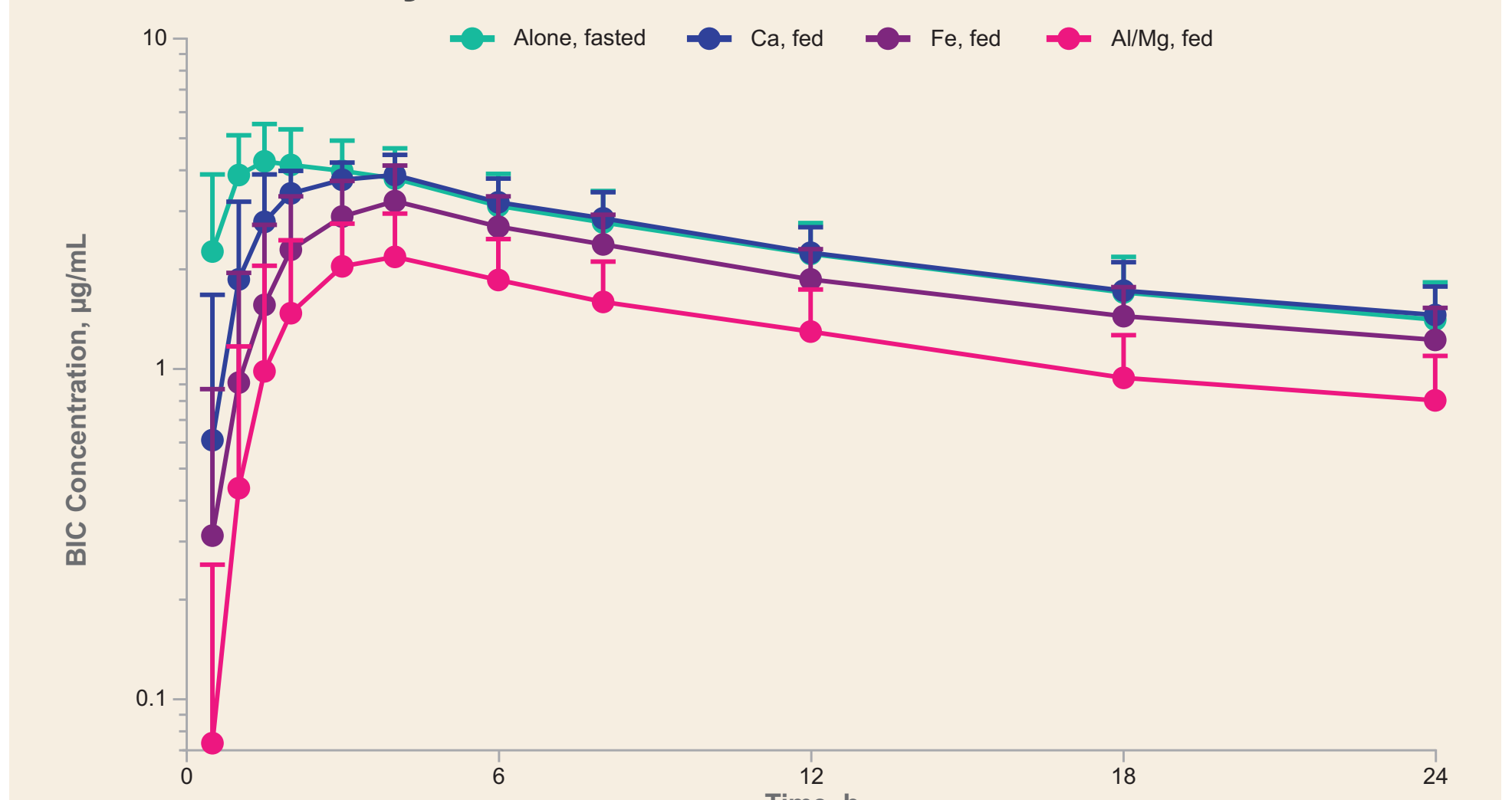
- Separation of B/F/TAF dose by as little as 2 h attenuated the chelating effect of PVCC antacids/supplements
 - Staggering of B/F/TAF 2 h before and 2 h after Al/Mg antacid administration resulted in modest decreases in BIC AUC_∞ (23% and 52%, respectively)

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

References: 1. Biktarvy [package insert]. Foster City, CA: Gilead Sciences, Inc.; Feb 2018. 2. Biktarvy [package insert]. Melbourne, Victoria, Australia: Gilead Sciences Pty Ltd.; July 10, 2018. 3. Biktarvy [product monograph]. Mississauga, Ontario, Canada: Gilead Sciences Canada, Inc.; July 10, 2018. 4. Biktarvy [SmPC]. Cambridge, UK: Gilead Sciences International Ltd.; 2018. 5. Daar E, et al. Lancet HIV 2018;5:e347-56. 6. Gallant JE, et al. Lancet 2017;390:2663-72. 7. Kiyoy C, et al. CROI 2018, abstr 500. 8. Molina JM, et al. Lancet HIV 2018;5:e357-65. 9. Sax PE, et al. Lancet 2017;390:2073-82. 10. Wohl DA, et al. IDWeek 2018, abstr LB4. 11. Lutz JD, et al. International Workshop on Clinical Pharmacology of Antiviral Therapy 2018, poster 6. 12. Aidsinfo. <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0>, May 30, 2018. 13. Genvoia [package insert]. Foster City, CA: Gilead Sciences, Inc.; Aug 2018. 14. Isentress [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2018. 15. Tivicay [package insert]. Research Triangle Park, NC: ViiV Healthcare; Sept 2018. Acknowledgments: We extend our thanks to the subjects and their families. This study was funded and conducted by Gilead Sciences, Inc.

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

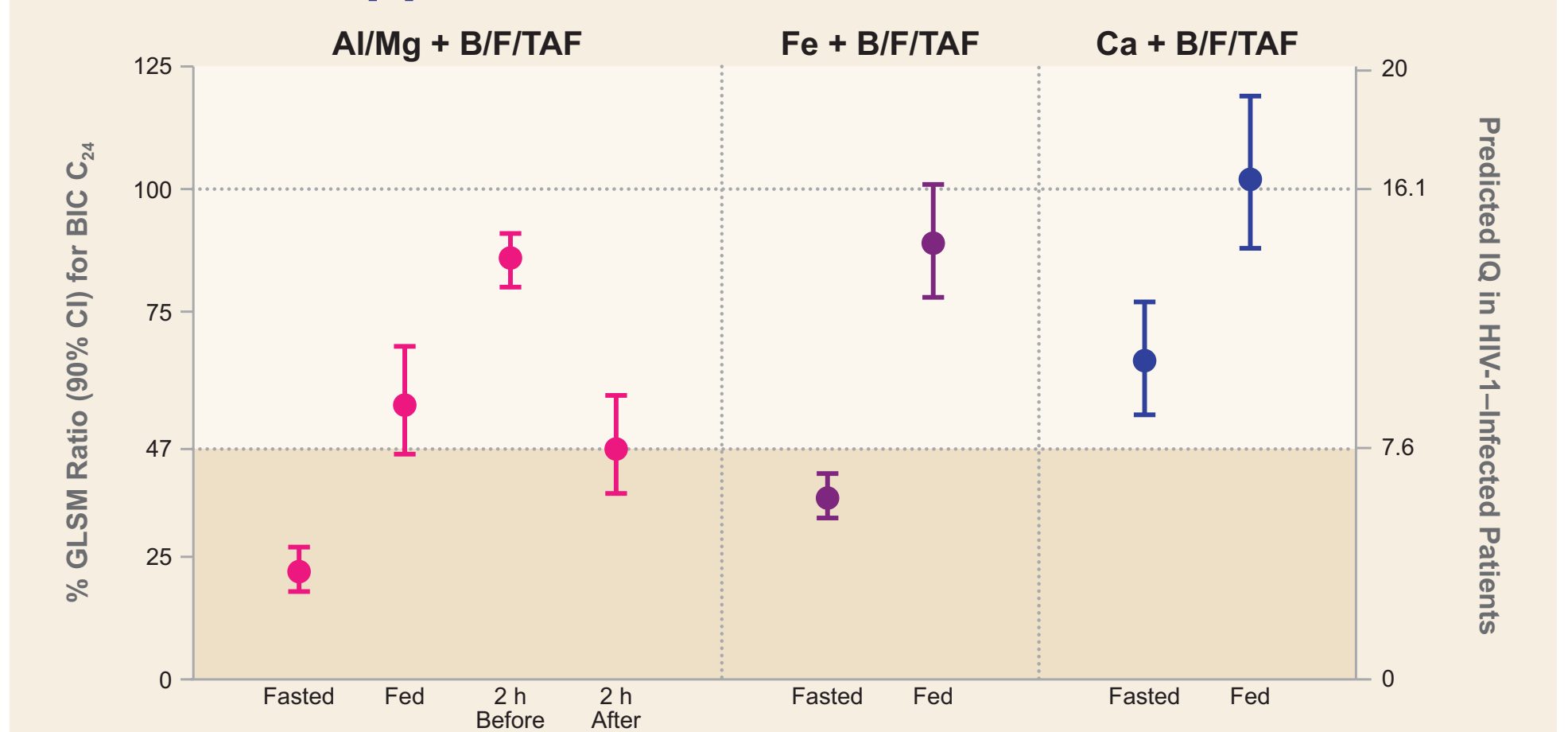


BIC PK Parameter, Mean (%CV)	Test n=14	B/F/TAF Alone, Fasted (reference) n=14	% GLSM Ratio (90% CI)
B/F/TAF fed + Al/Mg antacid (test)	AUC _∞ , h·µg/mL: 50.8 (34.8) C _{max} , µg/mL: 2.45 (31.4) C ₂₄ , µg/mL: 0.804 (36.4)	93.7 (27.2) 4.70 (23.6) 1.41 (29.7)	53.3 (44.2, 64.1) 51.5 (42.7, 62.0) 56.0 (46.2, 67.9)
B/F/TAF fed + Ca supplement (test)	AUC _∞ , h·µg/mL: 94.8 (21.2) C _{max} , µg/mL: 4.11 (13.7) C ₂₄ , µg/mL: 1.46 (22.1)	93.7 (27.2) 4.70 (23.6) 1.41 (29.7)	103 (89.0, 120) 89.6 (77.8, 103) 102 (88.1, 119)
B/F/TAF fed + Fe supplement (test)	AUC _∞ , h·µg/mL: 77.3 (24.8) C _{max} , µg/mL: 3.49 (23.2) C ₂₄ , µg/mL: 1.23 (25.0)	93.7 (27.2) 4.70 (23.6) 1.41 (29.7)	83.8 (74.1, 94.9) 75.1 (64.8, 87.1) 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

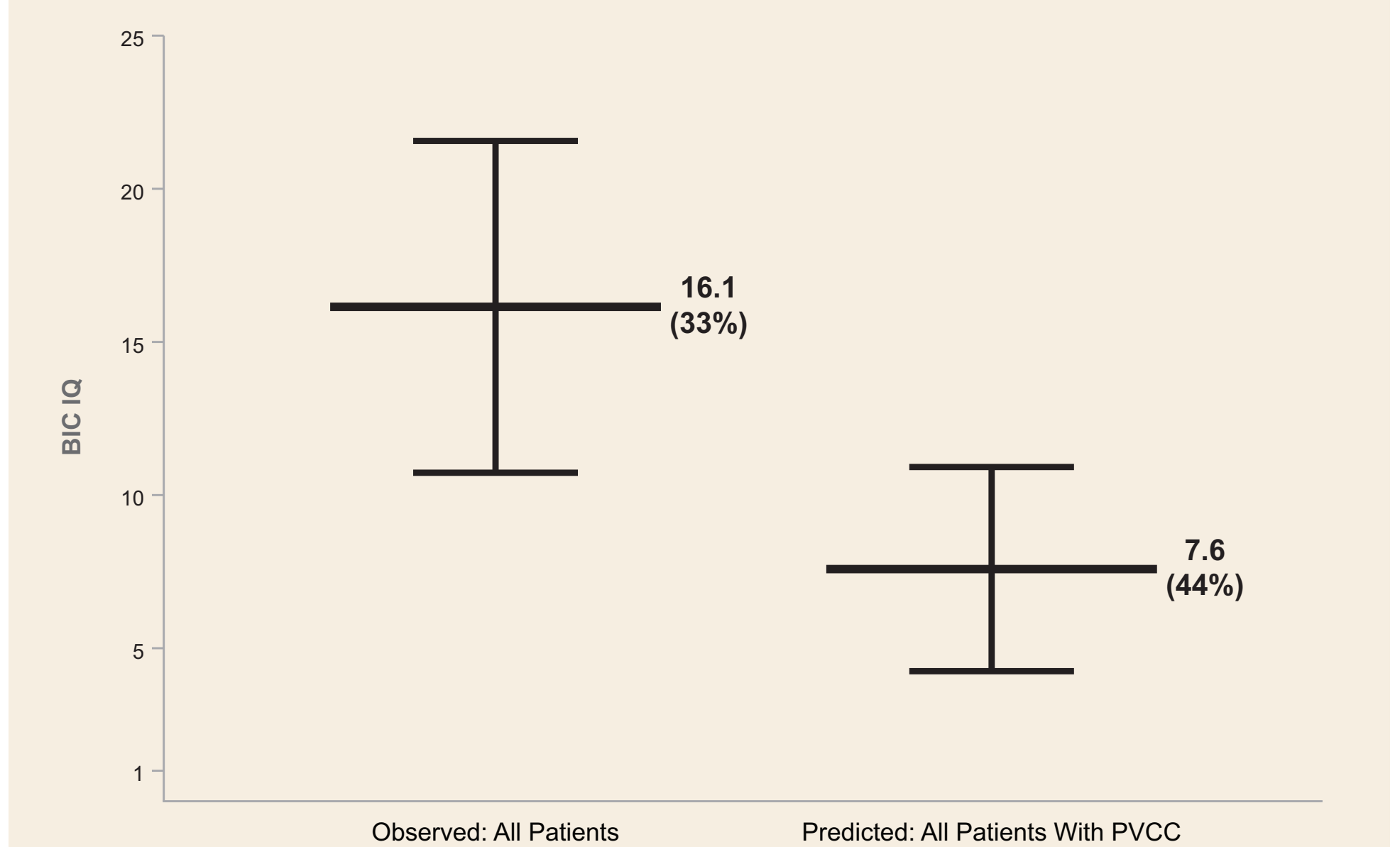
Summary of BIC C₂₄ Changes After Various PVCC Antacid/Supplement Coadministration Conditions*



*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 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 IQ values within the therapeutic window for HIV-1-infected patients, as previously defined¹¹

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%); BIC C₂₄ GLSM ratio was 0.47 and test C₂₄ 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%)