

Pharmacokinetics (PK) of Bictegravir (BIC) in Combination with Polyvalent Cation Containing (PVCC) Antacids and Supplements

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Background

- Polypharmacy is more common in People living with HIV than the general population¹
- Polyvalent cations (PVCs) may be used as antacids or supplements from both physician prescribed and OTC products or supplements
 - May include Magnesium, Aluminium, Iron (Ferrous) and Calcium
- PVCs may cause DDIs primarily through chelation with other drugs
 - Formation of insoluble complexes leading to impaired drug absorption
- INSTIs as a class are susceptible to DDIs with PVC primarily through chelation²⁻¹⁰

DDI, drug drug interactions; INSTI, integrase strand transfer inhibitors; OTC, over the counter

1. Lopez-Centeno B et al. HIV drug Therapy, Glasgow 2018, P211; 2. Cottrell ML et al. Clin Pharmacokinet. 2013 Nov;52(11):981-94; 3. Ramanathan S et al. J Acquir Immune Defic Syndr. 2013;64(1):45–50; 4. Krishna R et al. J Pharm Pharmacol. 2016 Nov;68(11):1359-1365. 5. Mathias A et al. HIV drug therapy, Glasgow 2018, P260; 6. E/C/F/TAF SmPC; 7. Raltegravir 400mg SmPC; 8. Raltegravir 600mg SmPC; 9. Dolutegravir 50mg SmPC; 10. B/F/TAF SmPC. All SmPCs accessed via www.medicines.org.uk on 30/3/19

Background (2)

- Bictegravir (BIC; B) is an un-boosted integrase strand transfer inhibitor (INSTI) with a high barrier to resistance
- Co-formulated with emtricitabine (F) and tenofovir alafenamide (TAF) into a single-tablet regimen (B/F/TAF)
 - BIC has demonstrated a wide therapeutic window²
 - BIC also susceptible to interaction with PVC³

Study Objectives

Primary Objective

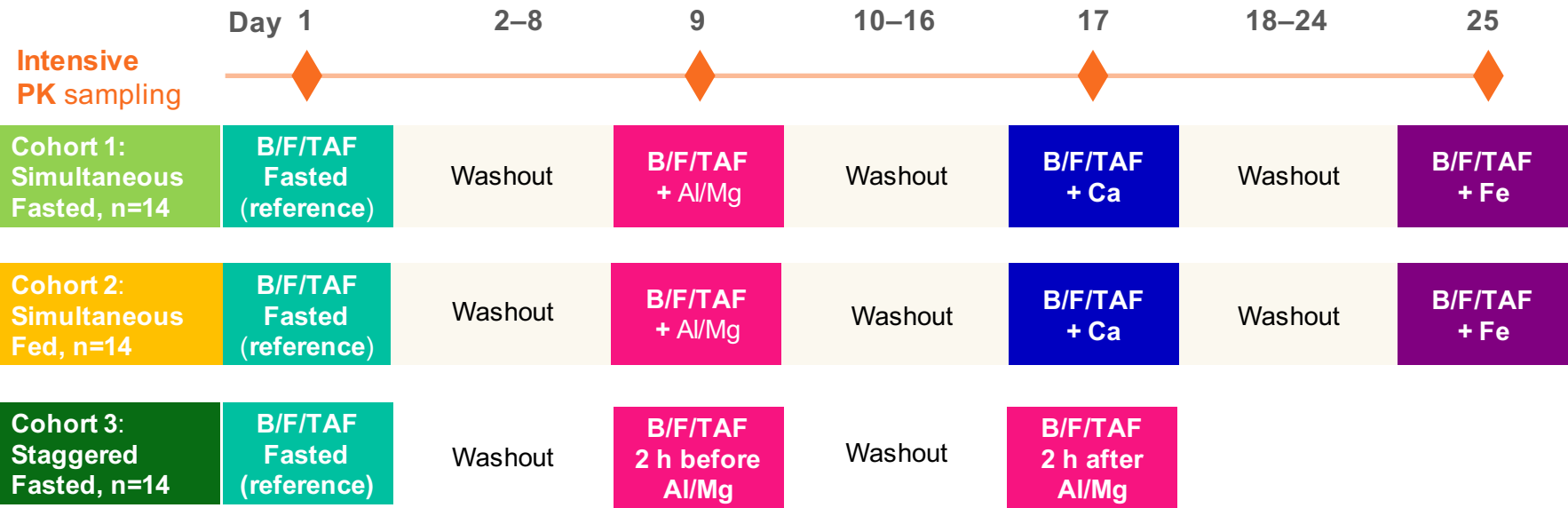
- Evaluate the effect of administration of aluminum/magnesium (Al/Mg) antacids and of calcium (Ca) or iron (Fe) supplements with B/F/TAF fixed-dose combination (FDC) on BIC pharmacokinetics (PK)
 - Can this potential effect be mitigated by food?
 - Can this potential effect be mitigated by staggered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

Secondary Objective

- Evaluate the safety and tolerability of B/F/TAF when given alone or in combination with Al/Mg antacids and Ca or Fe supplements

Methods: Study Design and Participant Cohorts

Phase 1, open-label, single-dose, fixed-sequence, multiple-cohort, multiple-period study in healthy participants



- 42 participants were enrolled
- All treatments were administered as single doses
- PVCC antacids and supplements tested were:
 - Antacid (aluminum hydroxide 1600mg, magnesium hydroxide 1600mg, simethicone 160mg)
 - Calcium carbonate (1200mg) supplement
 - Ferrous-fumarate (324mg) supplement

Methods – Safety and PK Analyses

Pharmacokinetic Analyses

- PK parameters (mean [%CV]) include
 - Area Under the Curve (AUC_{∞} [h·ng/mL]),
 - Maximal concentration (C_{max} [ng/mL])
 - Concentration 24 hours post-dose (C_{24} [ng/mL])
 - Projected Inhibitory Quotient (IQ)
- BIC exposures from test treatments were compared with the reference treatment as geometric least-squares mean (GLSM) ratios and associated 90% confidence intervals.
- The lack of drug-drug interaction boundary was 70% to 143%
- Safety
 - Adverse event (AE) monitoring, clinical laboratory assessments and physical examinations were performed throughout the study and follow-up

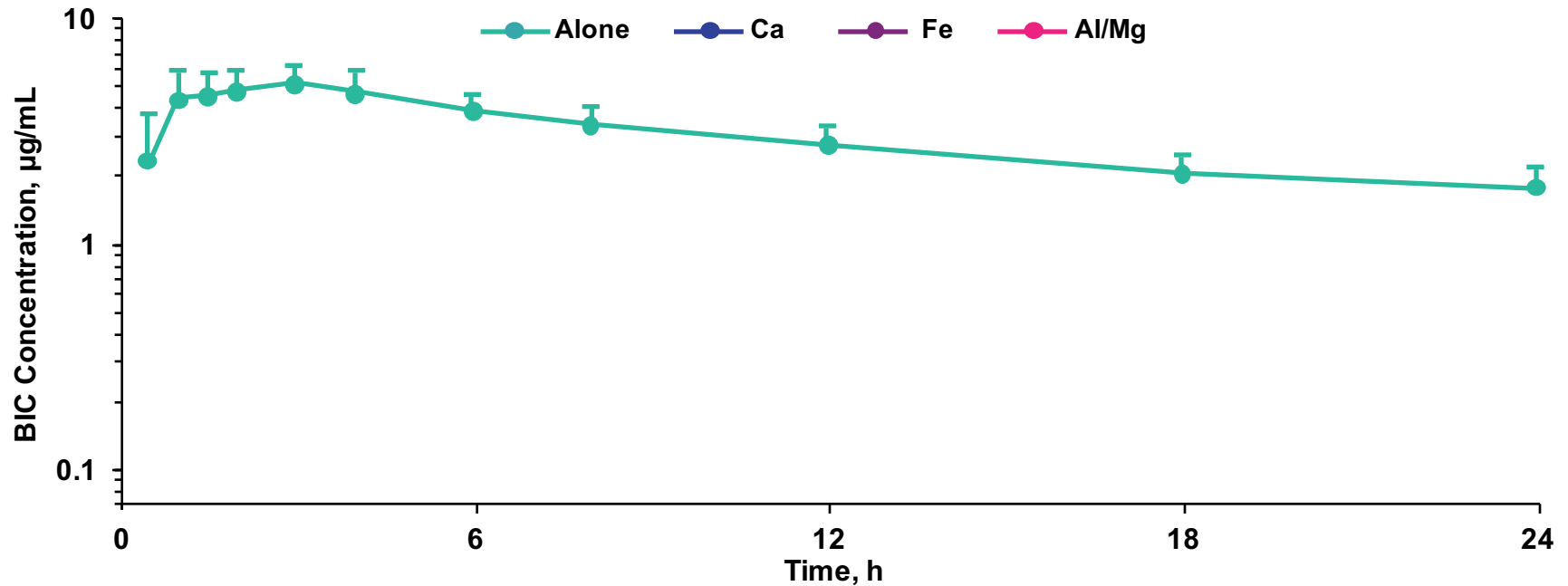
Results: Baseline Characteristics

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

Results – Safety and Tolerability

- All treatments were generally well tolerated
- 41/42 participants completed the study
 - 1 discontinuation due to Grade 2 urticaria which resolved on day 7
 - All AEs were Grade 1 or 2 in severity
 - Constipation observed was thought to be associated with use of antacids/Ca supplements
 - There were no clinically significant changes from pre-dose in median values for haematology or clinical chemistry parameters for any treatment

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



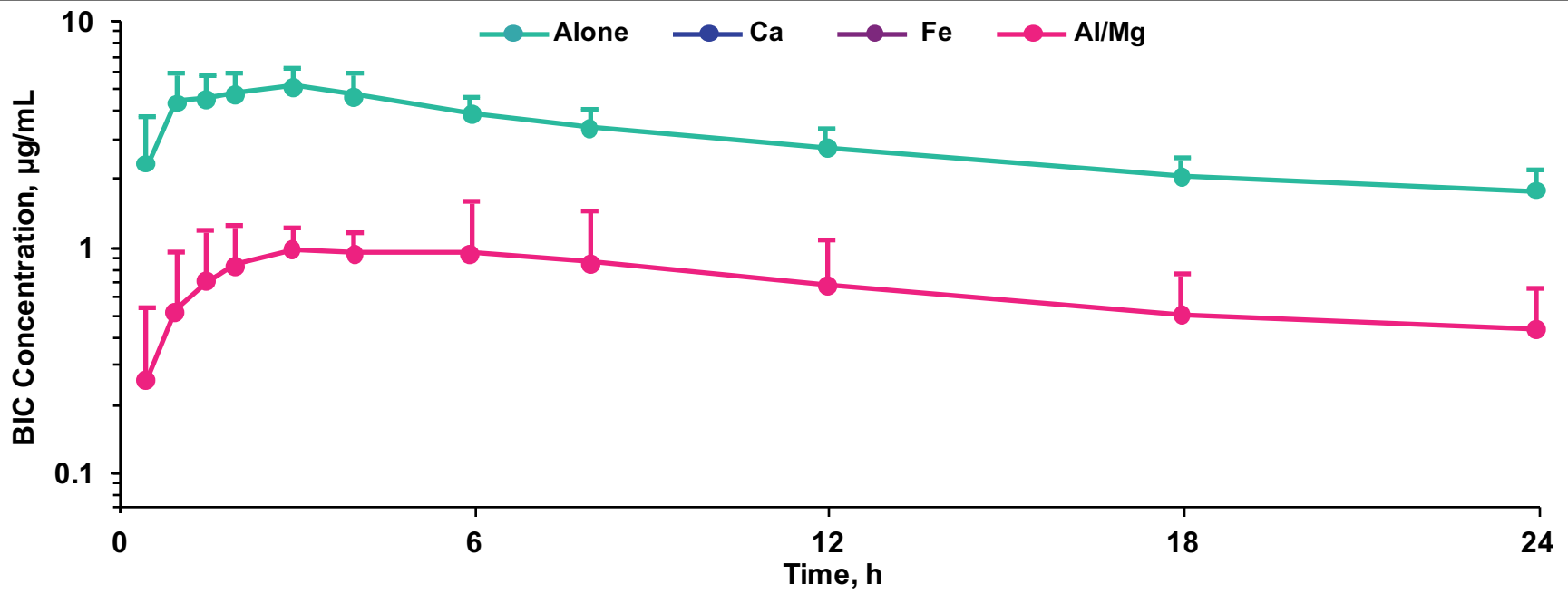
BIC PK Parameter,
Mean (%CV)

Test
n=14

B/F/TAF Alone,
Fasted (reference)
n=14

% GLSM Ratio
(90% CI)

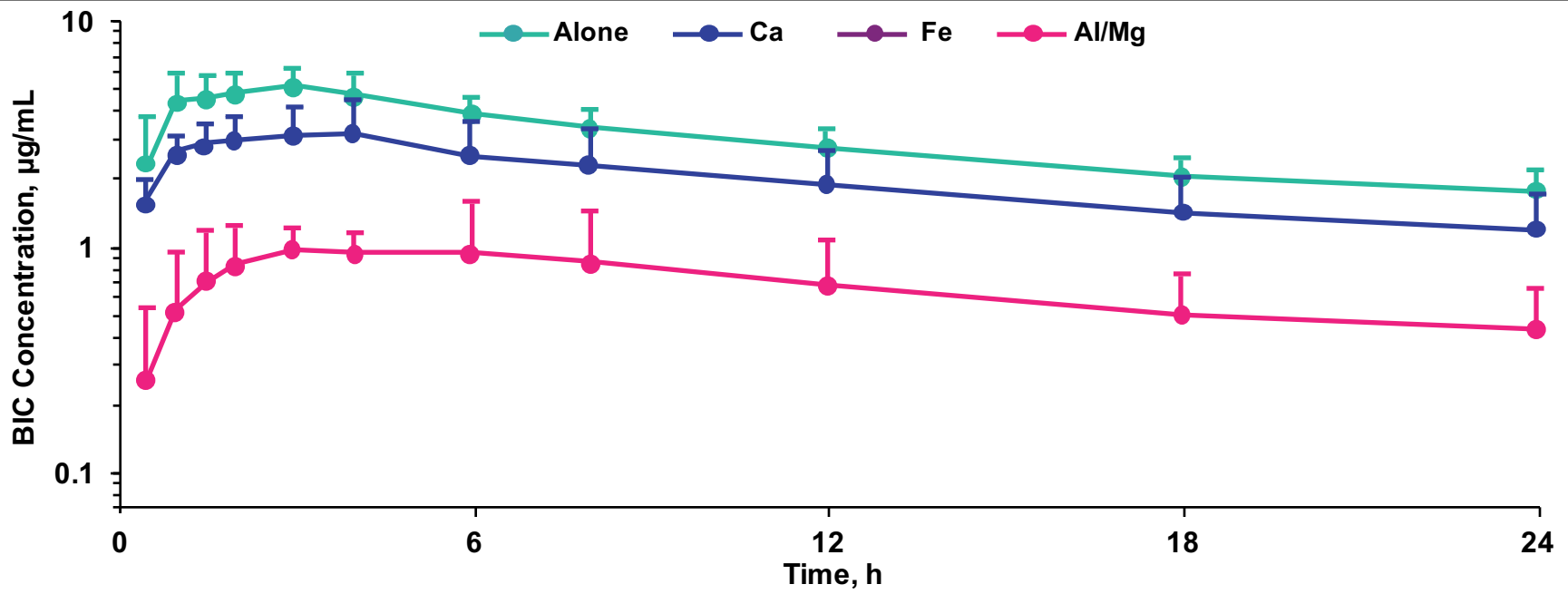
Effects of PVCC Antacids and Supplements on BIC Exposure Simultaneously, Fasted



| | 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) |

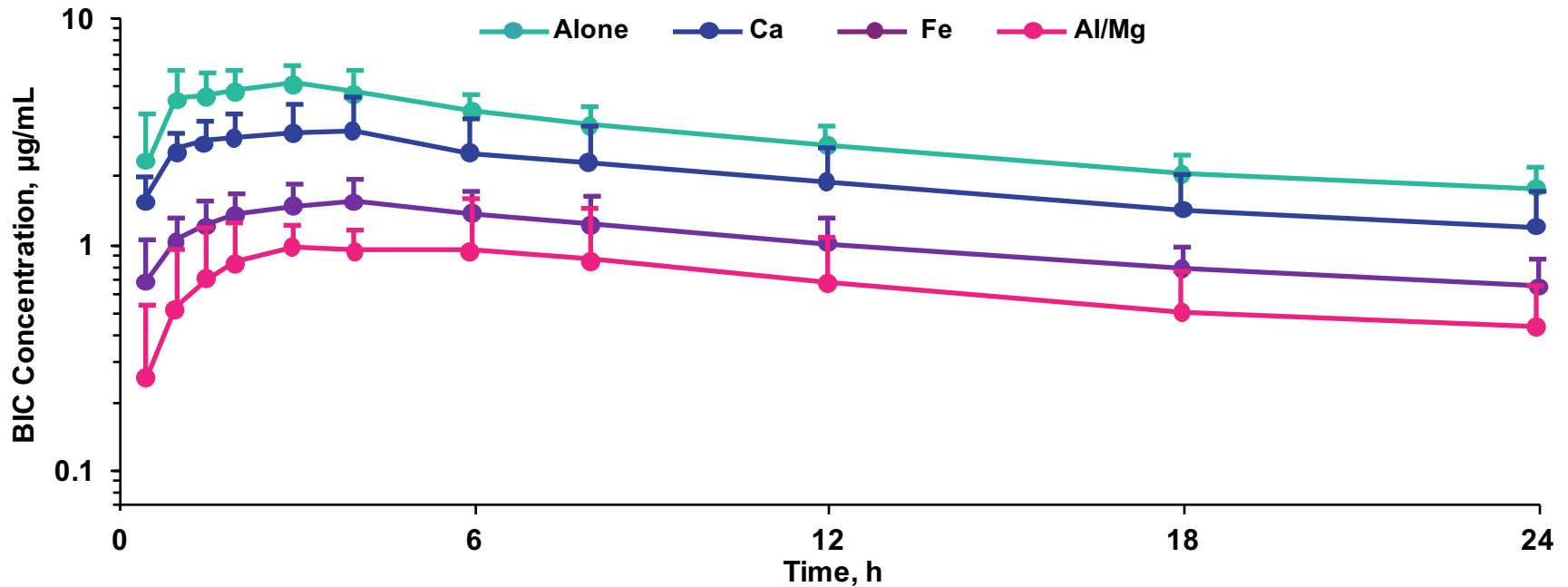
Al/Mg, B/F/TAF administered fasted with Al/Mg antacid; Alone, B/F/TAF administered fasted alone; Ca, B/F/TAF administered fasted with Ca supplement; Fe, B/F/TAF administered fasted with Fe supplement
 Kabagambe et al. BHIVA 2019, O08

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



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| B/F/TAF fasted+ Ca supplement (test) | AUC _∞ , h·µg/mL | 85.0 (43.1) | 122 (24.4) | 66.7 (56.7, 78.4) |

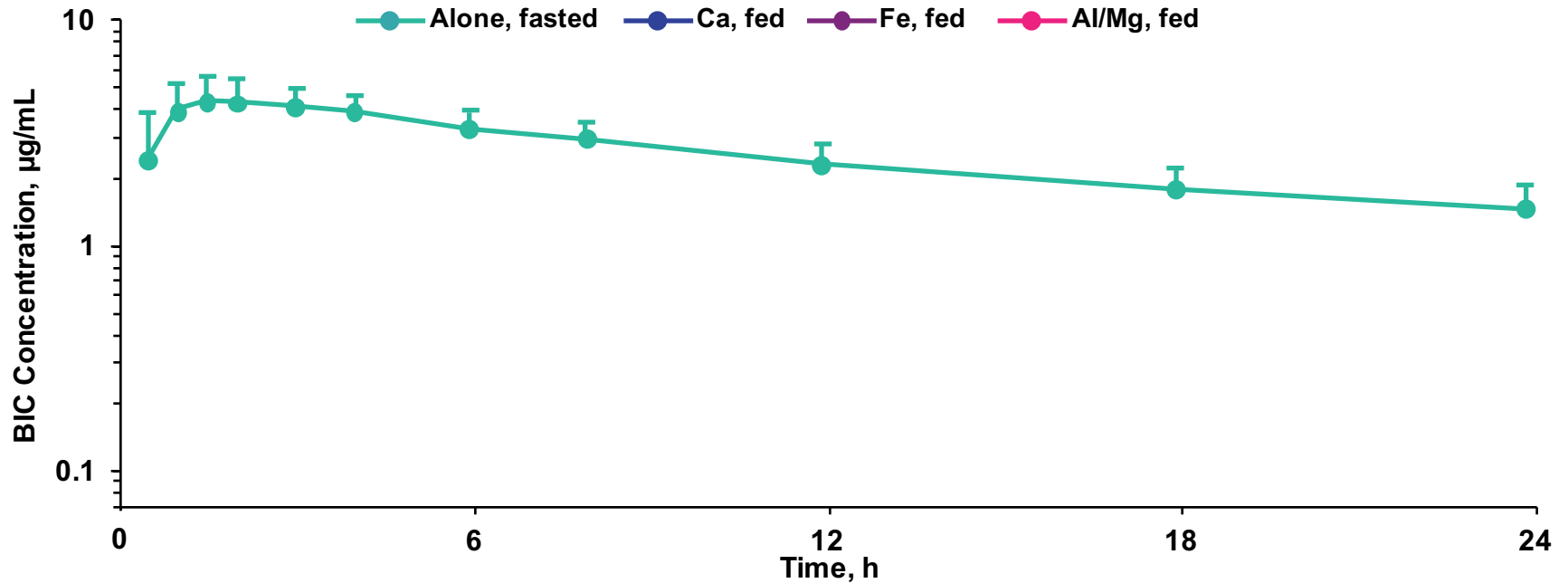
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| B/F/TAF fasted+ Ca supplement (test) | AUC _∞ , h·µg/mL | 85.0 (43.1) | 122 (24.4) | 66.7 (56.7, 78.4) |
| B/F/TAF fasted+ Fe supplement (test) | AUC _∞ , h·µg/mL | 46.1 (32.9) | 122 (24.4) | 37.1 (33.0, 41.8) |

Simultaneous fasted co-administration of B/F/TAF with Al/Mg and Fe-containing antacids/supplements is not recommended

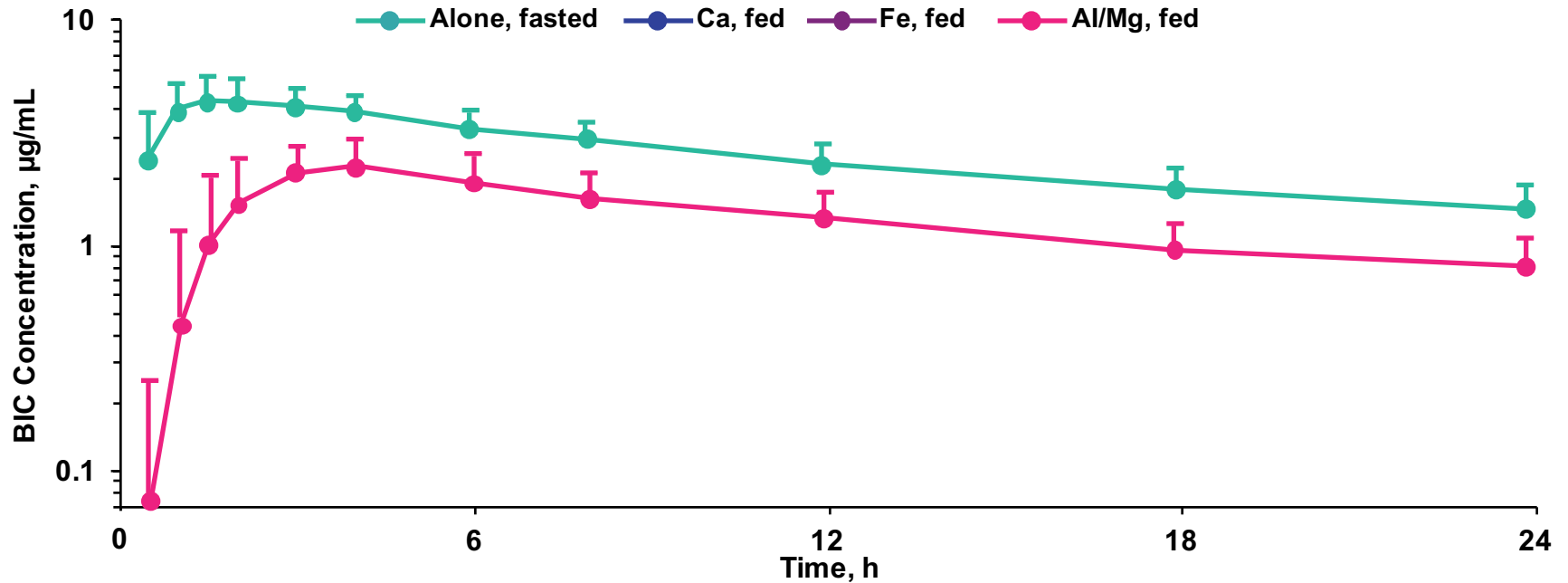
Effects of PVCC Antacids and Supplements on BIC Exposure Simultaneously, Fed



| BIC PK Parameter, Mean (%CV) | Test n=14 | B/F/TAF Alone, Fasted (reference) n=14 | % GLSM Ratio (90% CI) |
|------------------------------|-----------|--|-----------------------|
|------------------------------|-----------|--|-----------------------|

*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.

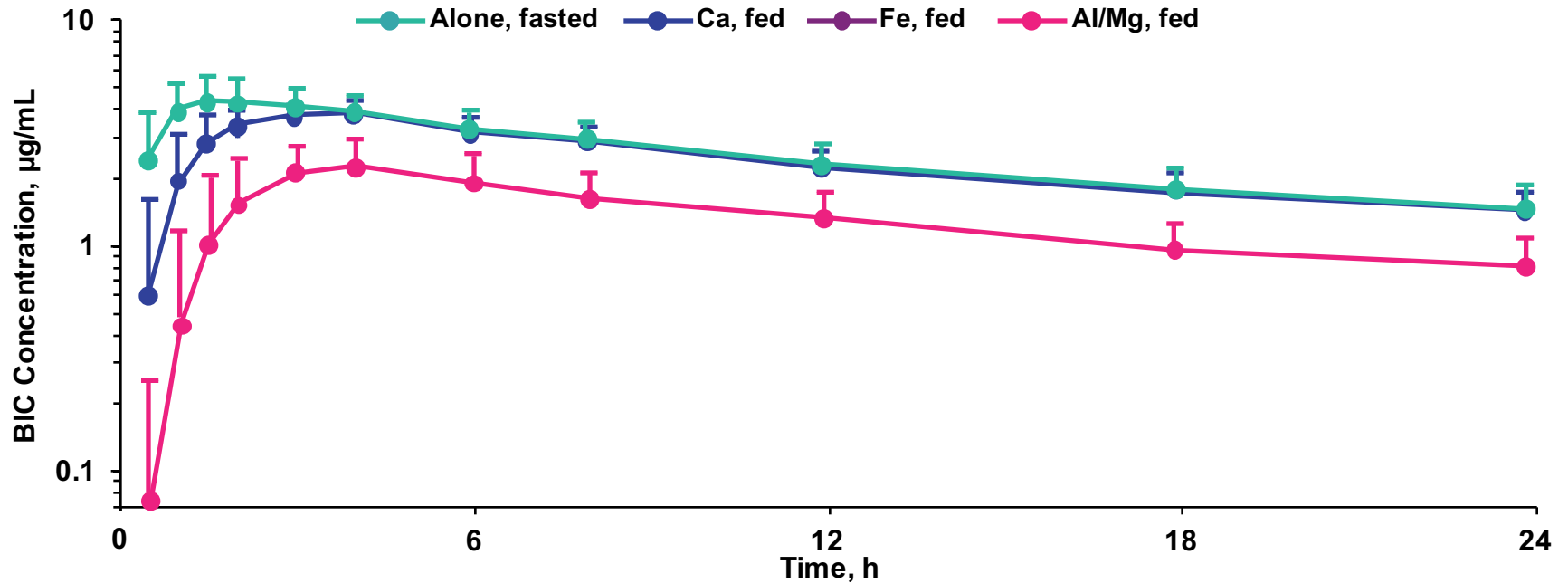
Effects of PVCC Antacids and Supplements on BIC Exposure Simultaneously, Fed



| | 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) |

*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.

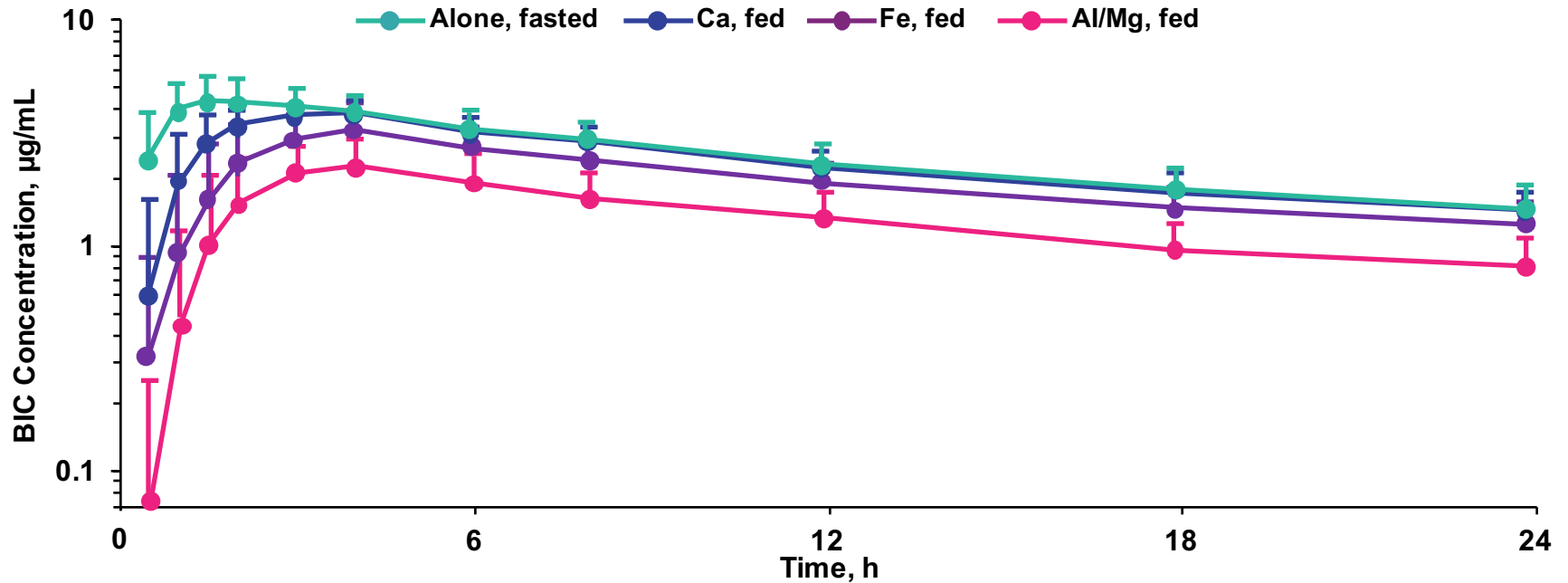
Effects of PVCC Antacids and Supplements on BIC Exposure Simultaneously, Fed



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| 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) |
| B/F/TAF fed + Ca supplement (test) | AUC _∞ , h·µg/mL | 94.8 (21.2) | 93.7 (27.2) | 103 (89.0, 120) |

*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.

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



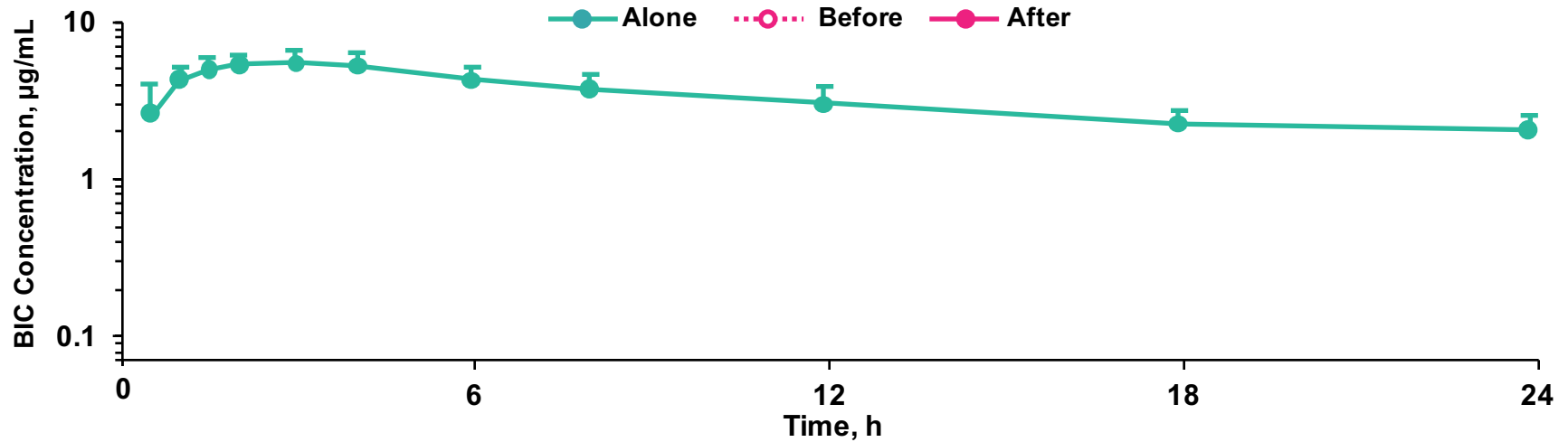
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| B/F/TAF fed + Ca supplement (test) | AUC _∞ , h·µg/mL | 94.8 (21.2) | 93.7 (27.2) | 103 (89.0, 120) |
| B/F/TAF fed + Fe supplement (test) | AUC _∞ , h·µg/mL | 77.3 (24.8) | 93.7 (27.2) | 83.8 (74.1, 94.9) |

Administration of food with B/F/TAF and Ca or Fe supplements mitigated chelating effect of PVCs

*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.

Effect of Al/Mg Antacids on BIC Exposure

Staggered, Fasted



BIC PK Parameter,
Mean (%CV)

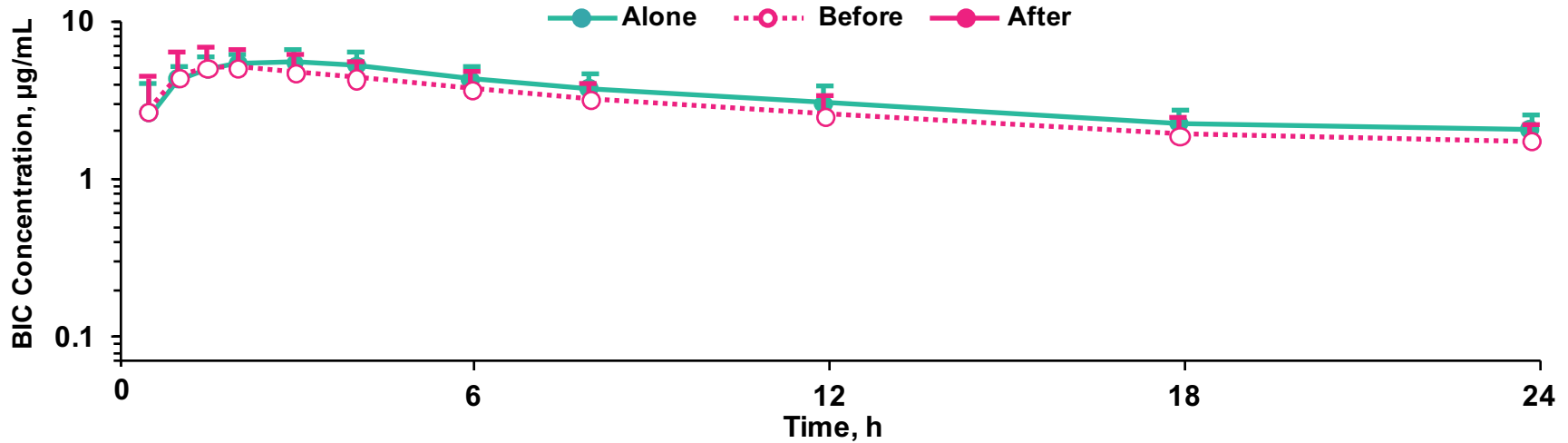
Test
n=13

B/F/TAF Alone,
Fasted (reference)
n=14

% GLSM
Ratio
(90% CI)

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.

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



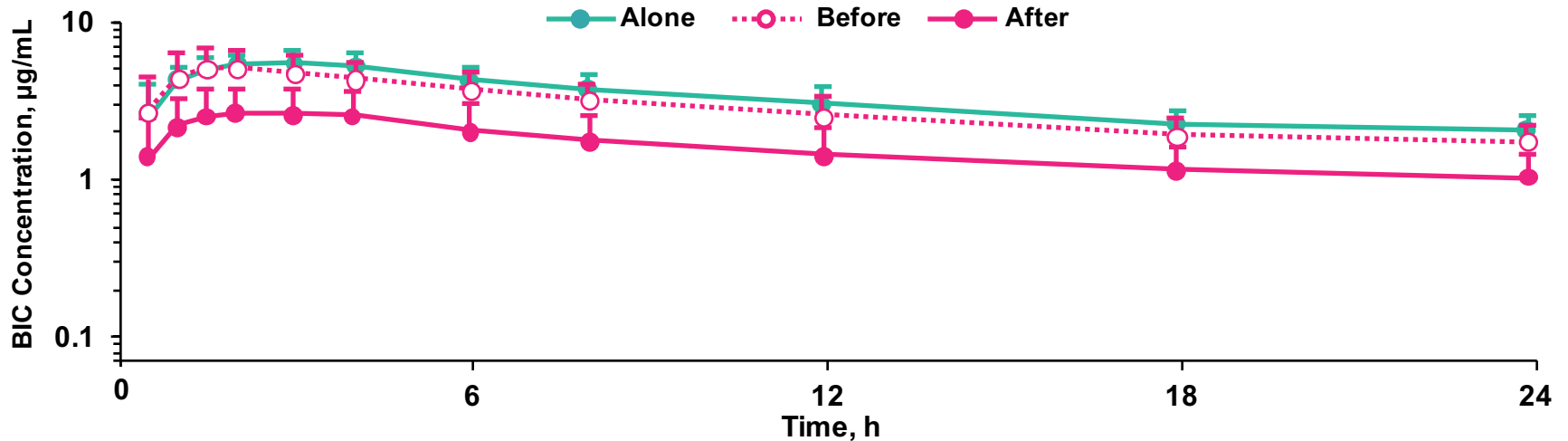
| BIC PK Parameter, Mean (%CV) | Test n=13 | B/F/TAF Alone, Fasted (reference) n=14 | % GLSM Ratio (90% CI) | |
|--|----------------------------|--|-----------------------|-------------------|
| B/F/TAF fasted 2h before Al/Mg antacid (test) | AUC _∞ , h·µg/mL | 116 (30.3) | 133 (27.0) | 86.7 (81.0, 92.8) |

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)

Separation of B/F/TAF dose by ± 2 hours attenuated the chelating effect of PVCC antacids/supplements

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.

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) |
| 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) |

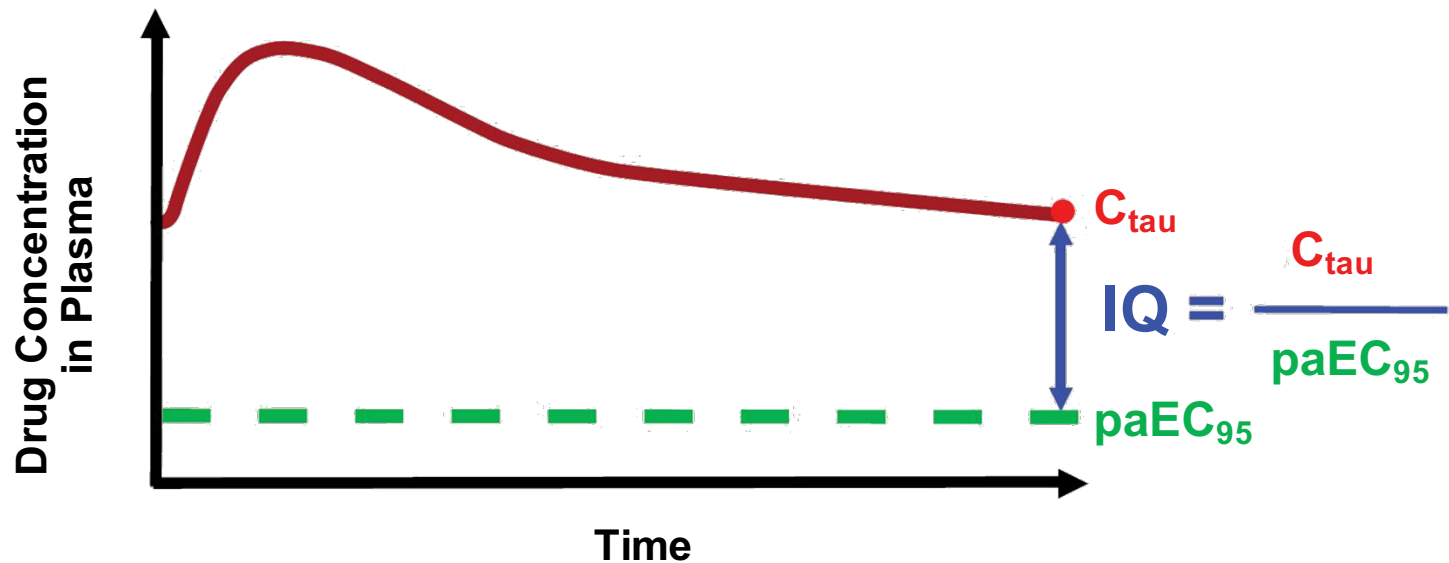
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After, B/F/TAF administered fasted 2 h after Al/Mg antacid; Alone, B/F/TAF administered fasted alone; Before, B/F/TAF administered fasted 2 h before Al/Mg antacid.

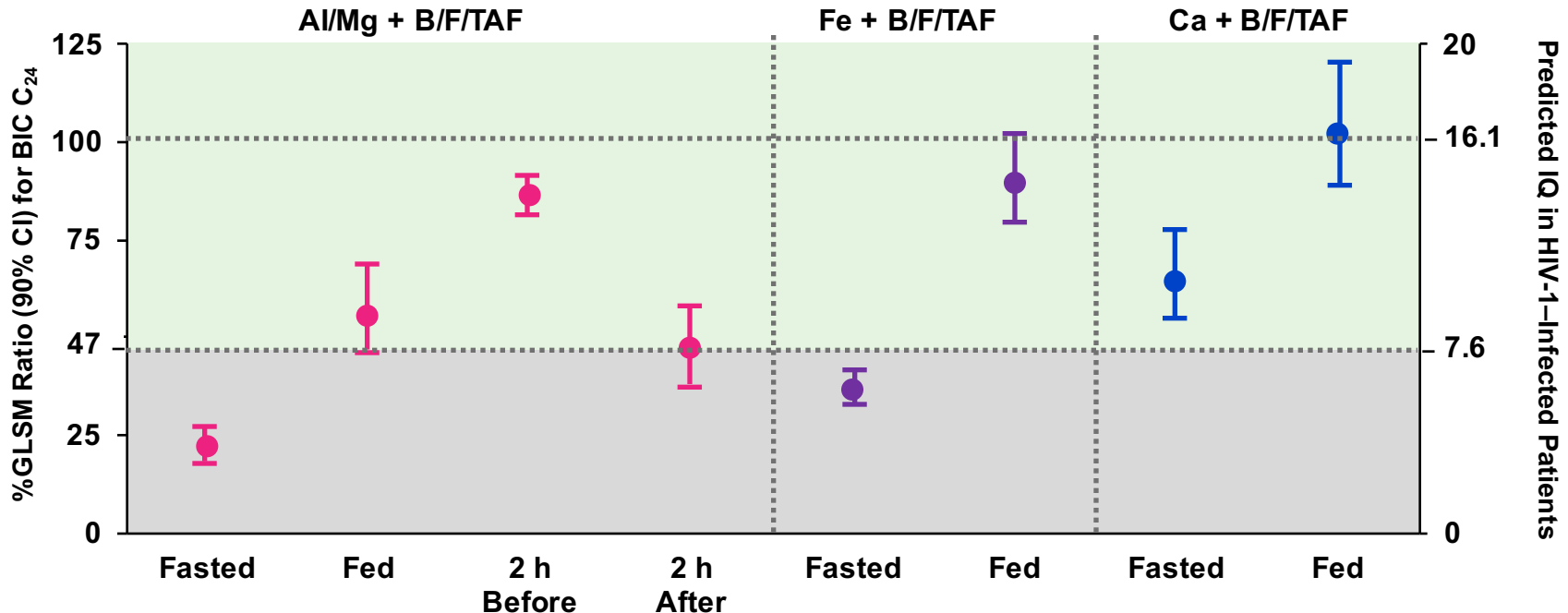
BIC Inhibitory Quotient

Drug Concentration Time-Curve at Steady State



- The number of times BIC C_{τ} (2.61 mcg/mL) is above the BIC $paEC_{95}$ (0.162 mcg/mL)
- A high mean inhibitory quotient (IQ) of **16.1*** was observed for BIC in the registration Phase 3 studies of B/F/TAF (N=584)

Summary of BIC C₂₄ Changes After Various PVCC Antacid/Supplement Co-administration Conditions*

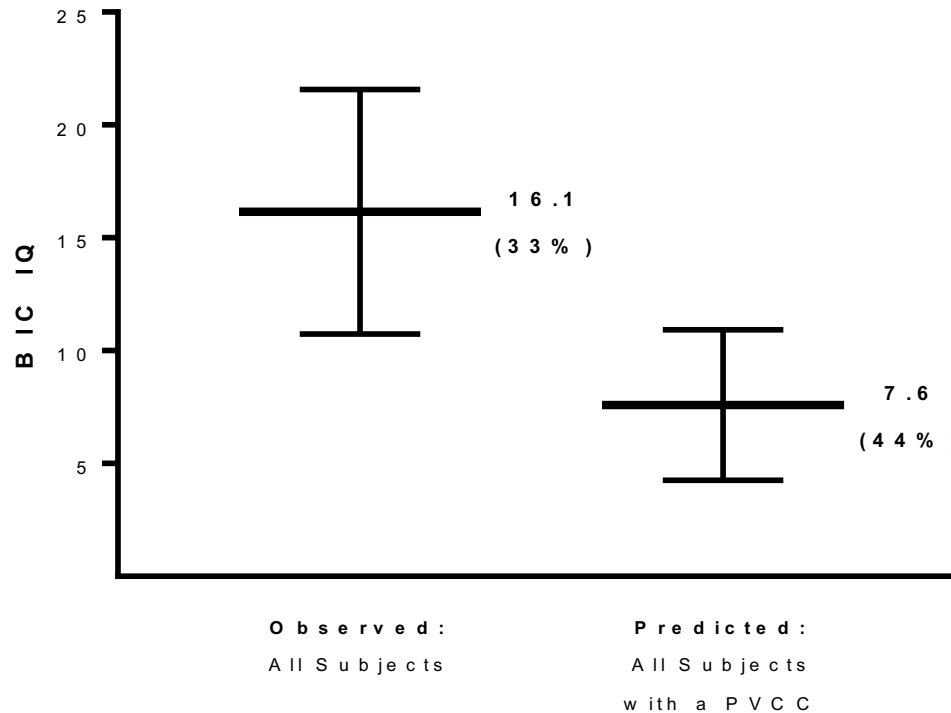


The effects on BIC PK and IQ were limited when PVCC antacids/supplements were administered either simultaneously with B/F/TAF under fed conditions or staggered from B/F/TAF administration by ± 2 h under fasted conditions

- Both coadministration conditions are expected to yield BIC IQ values within the therapeutic window for HIV-1–infected patients, as previously defined¹

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

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



The analysis suggested 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%)

*Mean IQ (%CV) in Phase 3 registrational studies was 16.1 (33%)¹¹; 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.

Conclusions

- Decreased BIC exposure from chelation by PVCC antacids/supplements can be attenuated by staggering administration \pm 2 hours and/or administering with food
- Mean IQ of 7.6 is predicted in HIV-1–infected patients co-administering B/F/TAF in a fasted state 2h after PVCC antacid/supplement therapy
 - Reduction in BIC exposure (IQ <1) is unlikely
- European B/F/TAF SmPC recommendations¹:
 - Al/Mg: B/F/TAF should be administered at least 2 hours before, or with food 2 hours after antacids containing Al or Mg
 - Iron: Take B/F/TAF at least 2 hours before iron supplements, or take together with food
 - Calcium: Can be taken together, without regard to food

Acknowledgments

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