Clinical Pharmacology of the Unboosted HIV Integrase Strand Transfer Inhibitor (INSTI) Bictegravir (BIC)

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Introduction

- Bictegravir (BIC; formerly GS-9883) is a novel, once-daily, INSTI
  - High barrier to resistance and potent in vitro activity against wild-type and most INSTI-resistant variants[1–4]
- A 10 day study of BIC monotherapy in HIV-1 infected subjects demonstrated rapid decline in HIV-1 RNA >2 $\log_{10}$[5]
- BIC single agent evaluated in Phase 2 in combination with emtricitabine (FTC) and tenofovir alafenamide (TAF)[6]
- BIC is in Phase 3 clinical development as a single-tablet regimen (STR) coformulated with FTC and TAF for the treatment of HIV-1 infection
- An extensive Phase 1 program characterized the clinical pharmacology of BIC

1. Jones G, et al. ASM Microbe 2016, poster 1673; 2. Lazerwith SE, et al. ASM Microbe 2016, poster 414; 3. Tsiang M, et al. ASM Microbe 2016, poster 1643; 4. White K, et al. 14th European Meeting on HIV & Hepatitis 2016, abstr O-01; 5. Gallant J, et al. ASM Microbe 2016, poster PW-030; 6. Sax P, et al. CROI 2017, abstract 41.

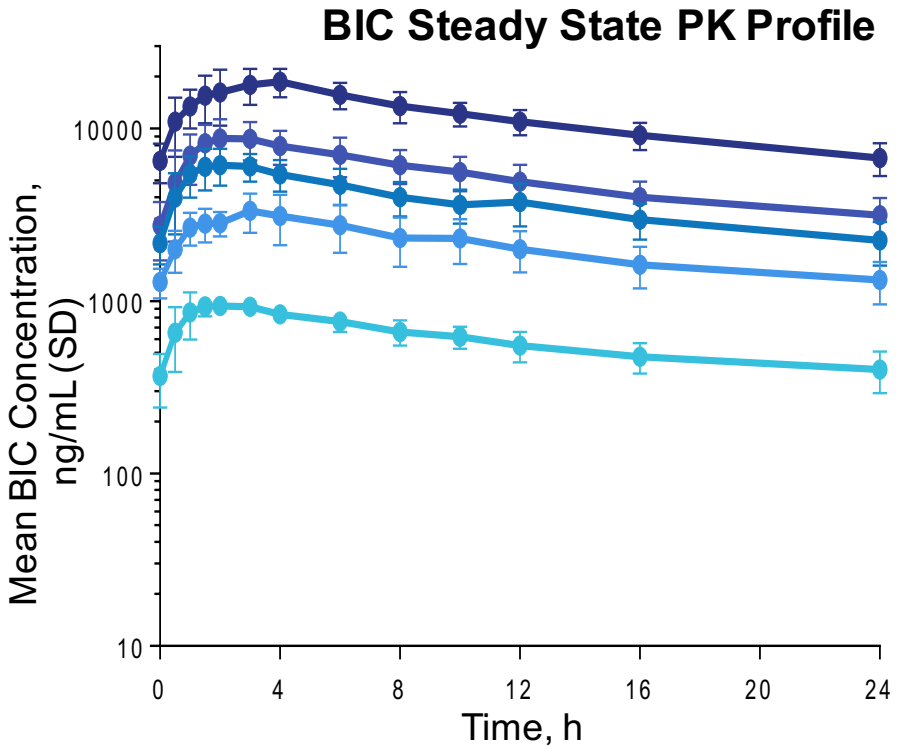
BIC Safety Profile from Phase 1 Program

- Generally well tolerated with no dose-dependent adverse events observed
  - Evaluated BIC doses of 5 to 100 mg in HIV-infected subjects and 5 to 600 mg in healthy subjects
- No effect on QT interval based on a negative thorough QT study
- No impact on glomerular filtration as measured by iohexol clearance

BIC Absorption, Distribution, Metabolism, Elimination (ADME)

- Well absorbed (>70%)
- Highly bound to plasma proteins (>99%)
- Primarily circulates as parent drug (BIC accounted for 68% plasma radioactivity)
- Metabolism is the major clearance pathway for BIC with similar contribution by oxidation (CYP3A4) and glucuronidation (UGT1A1)
  - Moderate hepatic impairment showed no clinically significant effect on PK
- Minimal renal clearance (~1% of unchanged parent excreted in urine)
  - No clinically significant effect of severe renal impairment ($eGFR_{CG}$ 15–30 mL/min) on PK

BIC Pharmacokinetic Profile Healthy Subjects



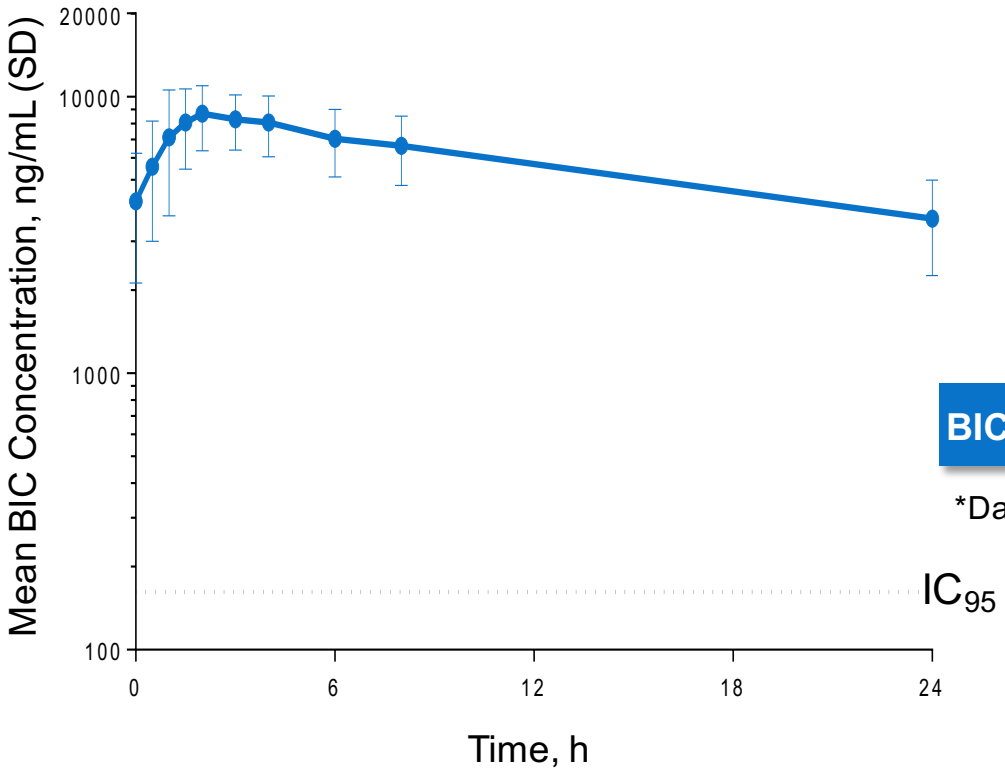
	BIC PK Parameters*		
	AUC_T, h·ng/mL	C_T, ng/mL	$t_{½}$, h
300 mg	277,000 (17)	6,760 (22)	18.1 (17.9, 20.5)
100 mg	127,000 (24)	3,150 (26)	18.9 (18.0, 20.0)
50 mg	89,700 (23)	2,240 (28)	16.7 (15.8, 17.1)
25 mg	50,000 (27)	1,320 (28)	18.1 (16.6, 19.6)
5 mg	14,400 (17)	401 (27)	18.5 (16.8, 20.0)

*Data presented as mean (%CV), $t_{1/2}$ median (Q1, Q3).

- $t_{½}$: ~18 hours
- PK profile supportive of once daily dosing
- PK profile consistent with that observed in HIV-infected subjects[1]

1. Gallant J, et al. ASM Microbe 2016, poster PW-030.

BIC Pharmacokinetic Profile HIV-infected Subjects Phase 2: BIC 75 mg + F/TAF 200/25 mg



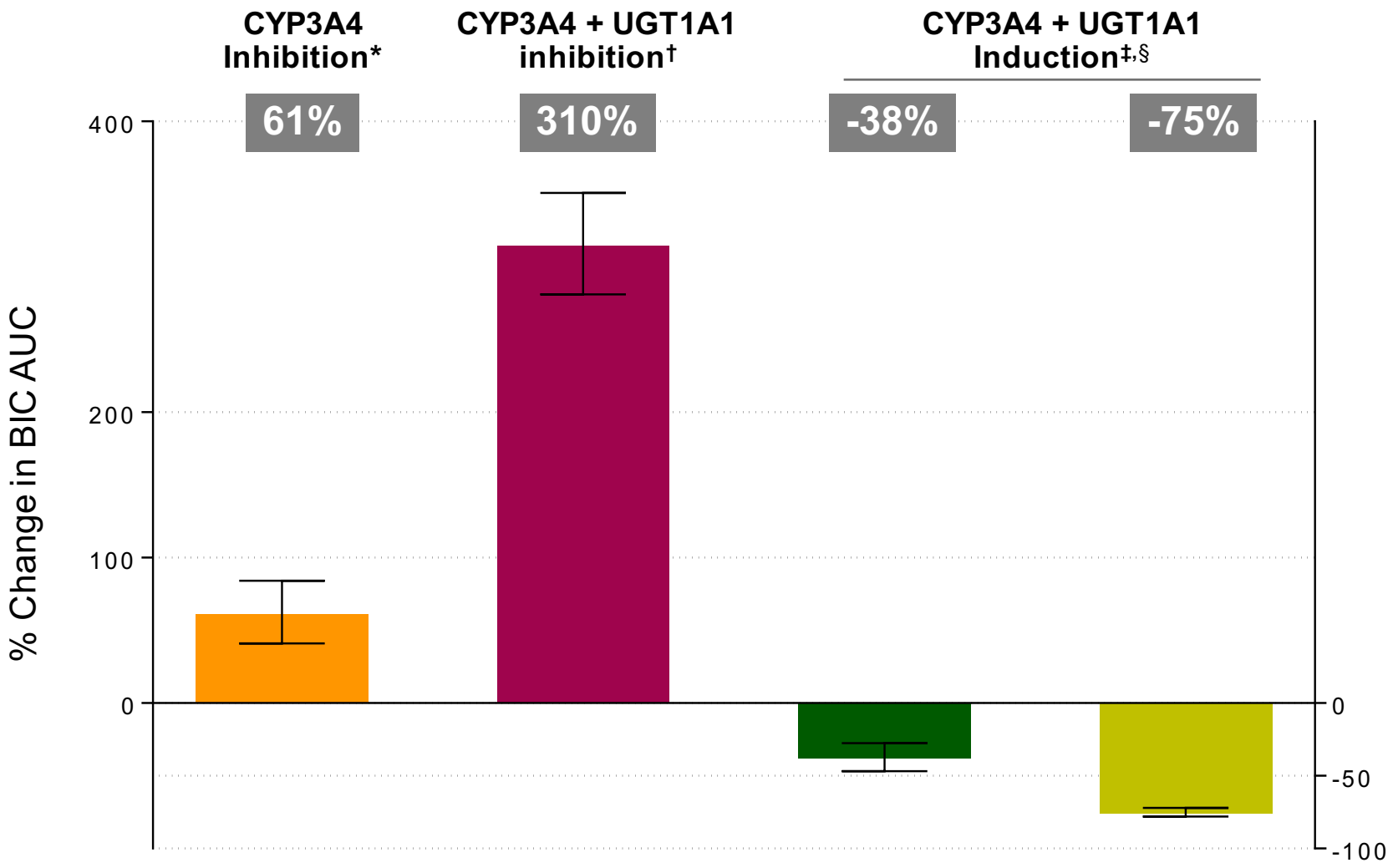
	BIC PK Parameters N=23		
	AUC_T, h·ng/mL	C_{max}, ng/mL	C_T, ng/mL
BIC 75 mg	140,000 (27)	9340 (27)	3510 (37)

*Data presented as mean (%CV).

BIC Drug-Drug Interaction (DDI) Profile

- Low potential as a victim of DDIs
  - INSTIs are affected by cation-containing antacids
    - BIC administration with antacids should be staggered (± 2 hours)
    - Fasted administration 2 hours before or 2 hours after antacid resulted in a decrease in BIC exposures of 13% and 52%, respectively
  - BIC is a substrate of CYP3A4 and UGT1A1
    - Inhibition of both CYP3A4 and UGT1A1 needed for substantial increase in exposure
    - Potent induction reduces exposure to a clinically significant extent

BIC Drug-Drug Interaction Profile
Clinical Study Probing Effect of Inhibitors or Inducers



*Voriconazole; †atazanavir; ‡rifabutin; §rifampin.

BIC Drug-Drug Interaction Profile

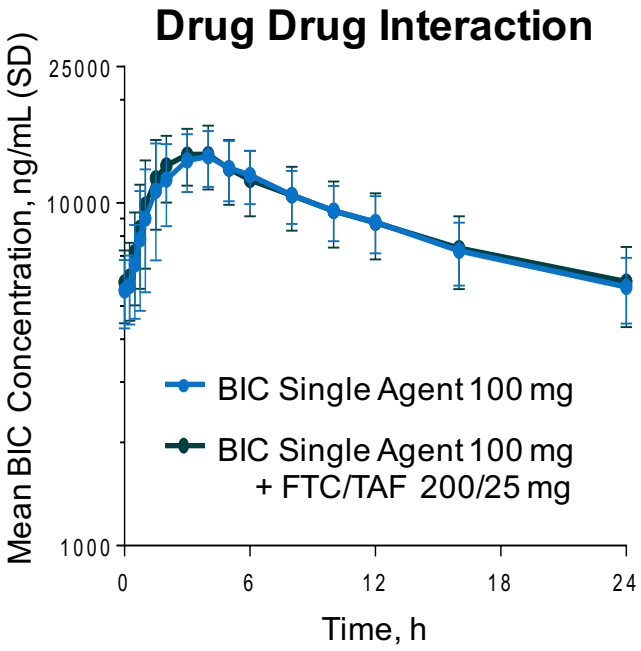
Effect of BIC on the PK of Coadministered Drugs

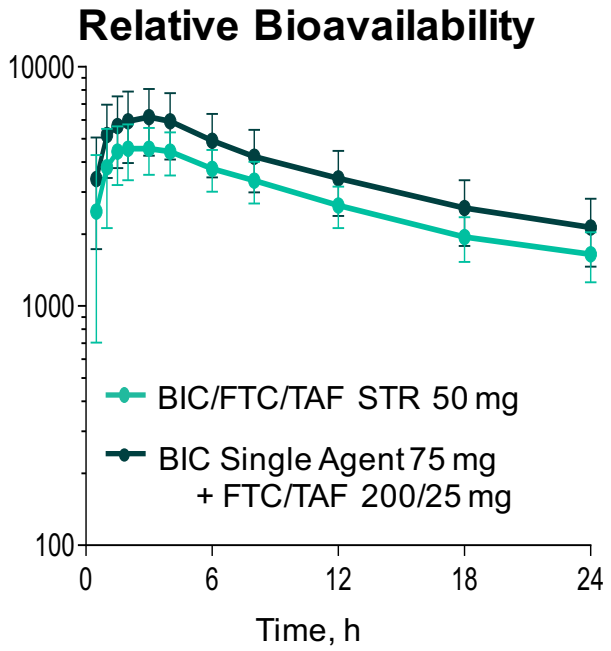
		Change in AUC
CYP3A4 Probe Substrate	Midazolam	↔
Representative Oral Contraceptive	Norelgestromin*	↔
	Ethinyl Estradiol	↔
Representative HCV DAA	Ledipasvir	↔
	Sofosbuvir	↔
OCT2/MATE1 Probe Substrate	Metformin	↑ 39%

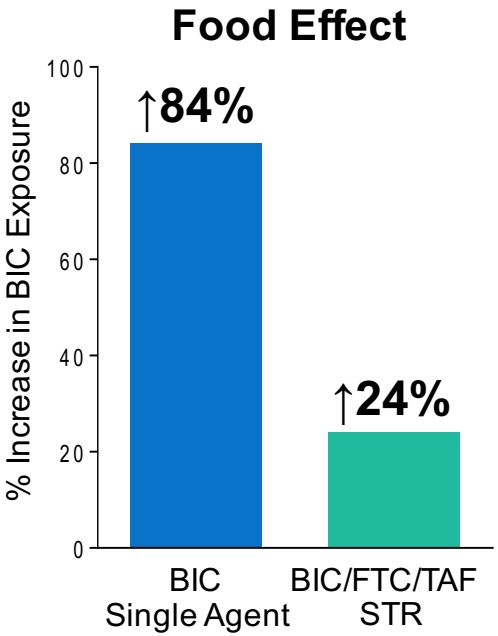
- Low potential to perpetrate DDIs
  - Not an inhibitor or inducer of CYP3A4 or UGT1A1
    - No effect on midazolam
  - No interaction with a representative oral contraceptive
    - No effect on norgestimate/ethinyl estradiol
  - No interaction with a representative HCV DAA
    - No effect on ledipasvir/sofosbuvir
  - Limited liability for inhibition of renal transporters (OCT2 and MATE1)
    - Modest increase in metformin exposure

*Norelgestromin is circulating pharmacologically active progestin from norgestimate.
90% CI of GMR were within (↔) or extended above (↑) the predetermined protocol defined equivalence boundaries of 70–143%.

Coformulation of BIC + F/TAF into Single Tablet Regimen (STR)







- Lack of DDI between BIC and FTC/TAF established
  - FTC/TAF 200/25 mg dose
- STR formulation development
  - Improved BIC bioavailability vs single agent Phase 2 formulation
  - Reduced food effect vs single agent Phase 2 formulation
  - STR with 50 mg BIC dose selected for Phase 3; administered with or without food

Conclusions

- Bictegravir is an INSTI with pharmacokinetics supportive of once daily dosing and a favorable DDI profile
- Coformulated BIC/FTC/TAF 50/200/25 mg STR under evaluation in Phase 3 studies

Acknowledgements

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