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Antiviral Activity, Safety, and Pharmacokinetics of Bictegravir as 10-Day Monotherapy in HIV-1–Infected Adults

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Objective: To evaluate antiviral activity, safety, and pharmacokinetics of short-term monotherapy with bictegravir (BIC), a novel, potent HIV integrase strand transfer inhibitor (INSTI).

Design: Phase 1b, randomized, double-blinded, adaptive, sequential cohort, placebo-controlled study.

Methods: HIV-infected adults not taking antiretroviral therapy were randomized to receive BIC (5, 25, 50, or 100 mg) or placebo once daily for 10 days. Primary endpoint was time-weighted average change from baseline to day 11 ($DAVG_{11}$) for plasma HIV-1 RNA. HIV-1 RNA, adverse events (AEs), and laboratory assessments were evaluated through day 17.

Results: Twenty participants were enrolled (n = 4/group). Mean $DAVG_{11}$ ranged from −0.92 to −1.61 across BIC doses versus −0.01 for placebo. Significant reductions in plasma HIV-1 RNA from baseline at day 11 were observed for all BIC doses compared with placebo ($P < 0.001$); mean decreases were 1.45–2.43 $\log_{10}$ copies/mL. Increased BIC exposures correlated with increased reduction in plasma HIV-1 RNA from baseline on day 11. Three participants on BIC (50 or 100 mg) achieved plasma HIV-1 RNA <50 copies/mL by end of study. Median T_{max} ranged from 1.0 to 1.8 hours (day 1, postdose) and 1.3–2.7 hours (day 10), with median $t_{1/2}$ ranging from 15.9 to 20.9 hours. No participant developed primary INSTI-R substitution through day 17. BIC was well tolerated, with no discontinuations because of adverse events.

Conclusions: BIC is a novel, potent, unboosted INSTI that demonstrated rapid, dose-dependent declines in HIV-1 RNA after 10 days of monotherapy. BIC was well tolerated, and displayed rapid absorption and a half-life supportive of once-daily therapy in HIV-infected subjects.

Key Words: antiretroviral therapy, integrase strand transfer inhibitors, pharmacokinetics, bictegravir, integrase inhibitors, GS-9883

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INTRODUCTION

Integrase strand transfer inhibitor (INSTI)-containing regimens are widely recommended for the treatment of HIV-1 infection.[1,2] Three INSTIs are currently approved and available for use: raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG). RAL currently requires twice-daily administration and is not coformulated with NRTIs. EVG is available in 2 once-daily single-tablet coformulations, but it requires pharmacologic boosting by cobicistat, a strong inhibitor of CYP3A4, resulting in the potential for drug–drug interactions with medications primarily metabolized by CYP3A4. RAL and EVG have overlapping resistance profiles. DTG is a once-daily unboosted INSTI with a higher barrier to resistance than RAL or EVG and is available as a single agent or coformulated with abacavir/lamivudine. Abacavir is associated with risk of hypersensitivity reaction, requires pretreatment HLA-B*5701 testing, and has been associated with an increased risk of cardiovascular events in some epidemiologic studies.[3–8] DTG can be administered once daily but requires twice-daily administration in the setting of previous INSTI failure with resistance and with some coadministered medications.[9]

Bictegravir (BIC, GS-9883) is a novel, potent, once-daily, unboosted INSTI with a high in vitro barrier to resistance and in vitro activity against most INSTI-resistant variants, including several variants that demonstrate reduced susceptibility to DTG.[10–13] Pharmacokinetic (PK) studies showed that

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BIC has a half-life of ~18 hours, may be given without regard to food, is mainly cleared by metabolism with similar contributions of CYP3A4 and UGT1A1, and drug–drug interactions are limited to potent dual inhibitors of CYP3A4/UGT1A1 (eg, atazanavir) and strong inducers of CYP3A4 (eg, rifampin).[14,15] We conducted a placebo-controlled study evaluating the short-term antiviral potency of BIC at doses ranging from 5 to 100 mg daily in HIV-infected adults.

METHODS

Participants

HIV-infected adults between the ages of 18 and 65 years of age were eligible for this study. Participants had CD4 cell counts of >200 cells/μL, plasma HIV-1 RNA between 10,000 and 400,000 copies/mL (inclusive), and were either treatment naive or antiretroviral treatment-experienced but INSTI-naive. They could not have received any antiretroviral treatment within 12 weeks of screening and must not have any INSTI resistance-associated mutations on screening genotype. Participants were excluded if they were coinfected with hepatitis B or C. This study was conducted in accordance with Good Clinical Practice procedures, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the institutional review board at each site. All patients provided written informed consent before study entry. The study was registered with ClinicalTrials.gov (Identifier NCT02275065).

Study Design

This was a phase 1b, multicenter, randomized, double-blinded, adaptive, sequential cohort, placebo-controlled study of BIC monotherapy for 10 days. In the first part of the study, we randomized 10 participants 1:1 to cohort 1 (BIC 25 mg) or cohort 2 (BIC 100 mg). Within each cohort, participants were assigned in a 4:1 ratio to receive active BIC or matching placebo. After review of data from the first 2 cohorts, we randomized 10 additional participants 1:1 to cohort 3 (BIC 5 mg) or cohort 4 (BIC 50 mg). Within each cohort, participants were again assigned 4:1 to receive active BIC or placebo. All participants received BIC or placebo every 24 hours by mouth in the fasted state for 10 days and were followed for 7 days after the end of dosing. Study personnel observed all study drug dosing.

Antiviral Activity Assessments

We collected blood samples at screening, day 1 (baseline), and days 2, 3, 4, 7, 8, 9, 10, 11, 14, and 17 for plasma HIV-1 RNA quantification using the Roche TaqMan 2.0 assay, with a lower limit of detection of 20 HIV-1 RNA copies/mL (Roche Diagnostics, Branchburg, NJ). Whole blood was collected at screening and on days 1, 11, and 17 for genotypic and phenotypic analysis of HIV-1 integrase using the GeneSeqIN and PhenoSenseIN assays (Monogram Biosciences Inc., South San Francisco, CA).

Safety and PK Assessments

Safety evaluations included recording of adverse events (AEs), concomitant medications, physical examinations, laboratory evaluations, and 12-lead electrocardiograms. We collected intensive PK plasma samples on days 1 and 10, predose PK samples on days 7, 8, and 9, and single-point PK plasma samples on days 14 and 17 after the last dose on day 10. We analyzed plasma samples using a validated high-performance liquid chromatography–tandem mass spectrometry method to determine BIC concentrations at QPS laboratories (Newark, DE). Single-dose PK parameters included C_{max}, T_{max}, C_{last}, T_{last}, $AUC_{0\text{-}24}$; multiple-dose PK parameters included C_{max}, T_{max}, C_{last}, T_{last}, area under the concentration versus time curve $AUC_{0\text{-}last}$, $AUC_{0\text{-}24}$, C_{tau}, $t_{1/2}$, AUC_{tau}, Vz/F, CL_{ss}/F, AR_AUC

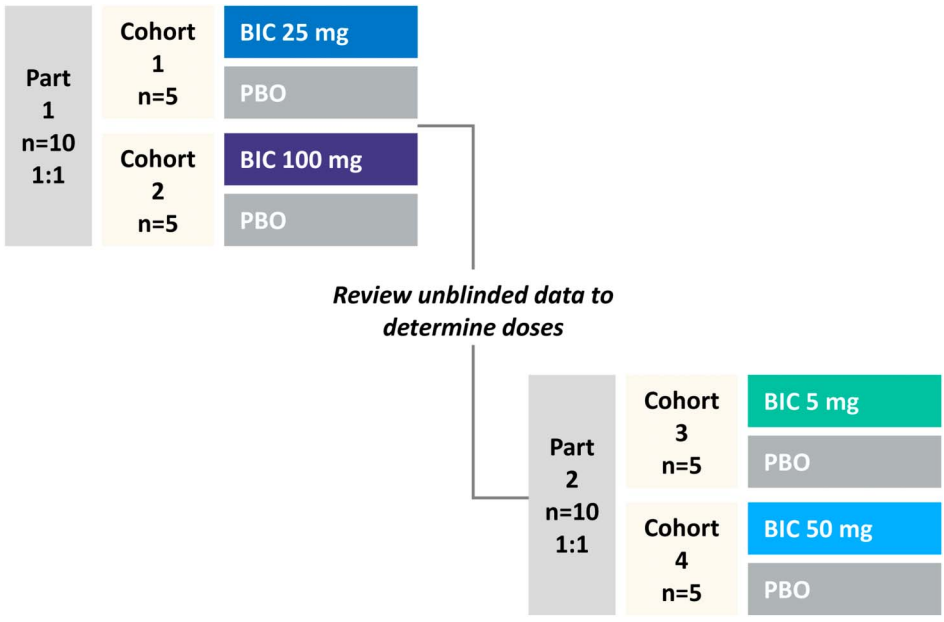

FIGURE 1. Study design. PBO = placebo.

(AUC accumulation ratio on day 10), AR_C_{max} (C_{max} accumulation ratio on day 10). PK parameters were estimated based on the observed concentration–time data by the non-compartmental PK approach using WinNonlin version 6.3 (Pharsight Corporation, Mountain View, CA). The $t_{1/2}$ values were determined using plasma concentrations through 168 hours (day 17) after the last dose on day 10.

Statistical Analyses

The primary efficacy endpoint was the time-weighted average change from baseline to study day 11 ($DAVG_{11}$) for plasma HIV-1 RNA. Participants were grouped according to actual treatment received, with all who received placebo combined as one treatment group for analysis purposes. The per-protocol analysis set was defined as all participants who took at least 1 dose of study drug and who had baseline HIV-1 RNA $\geq$1900 copies/mL, which allowed up to 2 $\log_{10}$ decreases in HIV-1 RNA. We determined that a planned sample size of approximately 4 participants per group in each active BIC group and 3 in the placebo-to-match group could provide 86% power to detect a treatment difference of 0.95 $\log_{10}$ copies/mL of $DAVG_{11}$ in HIV-1 RNA between at least 1 of the BIC treatment groups and the placebo group. In this power analysis, we assumed that a common SD for $DAVG_{11}$ in HIV-1 RNA was 0.32 $\log_{10}$ copies/mL (data on file) and that a 2-sided *t* test would be conducted at an alpha level of 0.05. For subjects in the per-protocol analysis set, we calculated $DAVG_{11}$ using the trapezoidal rule and the area under the curve concept. We summarized the $DAVG_{11}$ for plasma HIV-1 RNA by treatment and compared each active BIC treatment group with placebo group using the *t* test based on an analysis of variance model. In addition, we conducted a pairwise comparison among all active BIC treatment groups.

The maximum reduction from baseline in plasma HIV-1 RNA ($\log_{10}$ copies/mL) was calculated for the per-protocol analysis set using all available HIV-1 RNA data and was analyzed in the same fashion as for the primary efficacy endpoint. We fitted the viral decay slope using a log-linear regression model, where HIV-1 RNA collected at baseline (ie, the last available value before the first dose) and the last available on-treatment (ie, the last dose date +1) HIV-1 RNA value up to day 7 was used as the dependent variable. The collection days of these 2 HIV-1 RNA values was used as the independent variable. The viral decay slope was analyzed in the same fashion as for the primary efficacy endpoint. The percentage of participants ever achieving HIV-1 RNA $<$50 copies/mL after one dose of study drug and by the end of study was summarized by treatment group using the per-protocol analysis set. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

We used descriptive statistics for the safety analysis set, which included all who received at least one dose of study drug. AEs were coded with the Medical Dictionary for Regulatory Activities (version 17.1).

For the PK analyses, we used descriptive statistics to summarize plasma concentrations and PK parameters. In addition, we calculated geometric mean (95% CI) and mean (SD) of select natural-log transformed PK parameters. Dose proportionality of PK parameters of BIC was assessed by comparing PK parameters of BIC across all dose levels for single-dose (day 1) and multiple-dose (day 10), separately. In addition, dose proportionality was evaluated based on the power model and the analysis of variance method. The time to achieve steady-state plasma concentration of BIC within each cohort was evaluated using Helmert transformation testing procedure of C_{trough} on day 2, and days 7–11.[16]

RESULTS

Participants

We randomized 23 participants, of whom 3 were never treated. Twenty participants received study drug (4 in each BIC dose group and 4 in the placebo group, Fig. 1). Across all treatment groups, demographics and baseline characteristics were similar (Table 1). Most participants were men (95%) and white (65%); the mean age was 33 years (range 19–59 years). Participants had a mean body mass index of 25.4 kg/m^2 (range: 19.7–31.6 kg/m^2) and a mean estimated glomerular filtration rate

TABLE 1. Baseline Characteristics

	BIC					
Characteristics	**5 mg (N = 4)**	**25 mg (N = 4)**	**50 mg (N = 4)**	**100 mg (N = 4)**	**Placebo (N = 4)**	**Total (N = 20)**
Mean (range) age, yrs	29 (25–34)	44 (29–59)	34 (19–44)	36 (26–48)	24 (21–28)	33 (19–59)
Male, n (%)	4 (100)	4 (100)	3 (75)	4 (100)	4 (100)	19 (95)
Race, n (%)						
Black	0	1 (25)	1 (25)	1 (25)	3 (75)	6 (30)
White	4 (100)	2 (50)	3 (75)	3 (75)	1 (25)	13 (65)
Mean (SD) BMI, kg/m^2	27.5 (5.4)	26.9 (2.2)	22.5 (3.6)	27.4 (3.8)	22.7 (2.5)	25.4 (4.0)
Mean (SD) HIV-1 RNA ($\log_{10}$ copies/mL)	3.8 (1.0)	4.6 (0.5)	4.4 (0.5)	4.7 (1.0)	4.5 (0.4)	4.4 (0.7)
Mean (SD) CD4 cell count (/μL)	520 (138.0)	329 (98.1)	445 (123.8)	410 (215.1)	507 (112.7)	442 (146.0)
ARV status, n (%)						
ART naive	3 (75)	3 (75)	4 (100)	2 (50)	4 (100)	16 (80)
ART-experienced but INSTI-naive	1 (25)	1 (25)	0	2 (50)	0	4 (20)

ART, antiretroviral treatment.

by Cockcroft–Gault of 132.1 mL/min (range: 84.0–209.0 mL/min). The mean CD4 count was 442 cells/μL, and the mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL. At baseline, no participant had a primary INSTI resistance substitution in their HIV-1 RNA. At baseline, polymorphic integrase substitutions associated with INSTI resistance were present in 9 participants, with 7 having S119P and 2 having M50I.

Antiviral Activity

Administration of BIC led to a dose-dependent decrease in viral load. With increasing doses of BIC, the reduction of $DAVG_{11}$ in plasma HIV-1 RNA increased linearly, the maximum reduction of HIV-1 RNA from baseline increased, the viral decay slope steepened, and the reduction of plasma HIV-1 RNA at day 11 from baseline increased (Table 2, Fig. 2). Mean (SD) $DAVG_{11}$ in plasma HIV-1 RNA ($\log_{10}$ copies/mL) ranged from −0.92 (0.104) at 5 mg BIC to −1.61 (0.256) at 100 mg BIC, respectively, and was −0.01 (0.144) for the placebo group. All BIC groups experienced statistically significant differences compared with placebo in plasma HIV-1 RNA $DAVG_{11}$, maximum reduction from baseline, viral decay slope, and change from baseline at day 11 in plasma HIV-1 RNA (Table 2). Three participants who received BIC achieved plasma HIV-1 RNA less than 50 copies/mL; baseline viral load for each was 10,700 copies/mL (50 mg BIC), 15,800 copies/mL (100 mg BIC), and 3680 copies/mL (100 mg BIC).Post-treatment viral load declines continued through day 14 for the 50 mg dose group and through day 17 for the 100 mg dose group.

Pharmacokinetics

All 16 participants who received BIC had well-characterized plasma PK on days 1 and 10. The plasma concentration versus time profiles observed on day 10 after multiple-daily doses of BIC (5, 25, 50, and 100 mg) were similar to the plasma concentration versus time profiles observed after the first dose on day 1. Analyses of predose plasma concentrations on days 7–11 revealed that day 10 PK represented steady-state PK. BIC was rapidly absorbed as indicated by cohort median T_{max} between 1.0 and 1.8 hours after the first dose on day 1 and between 1.3 and 2.7 hours on day 10 (Table 3). Mean BIC exposure was approximately dose-proportional after single-dose administration of 5–50 mg on day 1 and multiple-dose administration of 5–100 mg on day 10. The cohort median $t_{1/2}$ determined using plasma concentrations 168 hours after the last dose ranged from 15.9 to 20.9 hours across dose groups, consistent with mean steady-state AUC accumulation ratios of cohorts ranging from 125% to 193%. The terminal phases across doses were approximately parallel until 96 hours after the day 10 dose, indicating no sign of clearance saturation in the dose range tested. The apparent steady-state clearance and volume of distribution were low, consistent with high plasma protein binding observed in vitro (99.7%).[17]

Antiviral Resistance

At screening, no isolate had a primary INSTI resistance substitution, and all were fully susceptible to BIC (median 0.97-fold change; range 0.59–1.32). Of the 16 subjects who received BIC, 10 participants had genotypic data available at days 11 and 17. No primary INSTI resistance substitutions emerged during the study. One isolate in the BIC 25-mg group had emergence of the polymorphic substitution M50M/I in integrase at day 11 that was not present at day 17, with no change in phenotypic susceptibility to BIC (1.2-fold at screening and 1.1-fold at day 11). No other INSTI

TABLE 2. Virologic Responses to Bictegravir and Viral Decay Slope

	BIC				
	5 mg (N = 3)*	**25 mg (N = 4)**	**50 mg (N = 4)**	**100 mg (N = 4)**	**Placebo (N = 4)**
Mean $DAVG_{11}$, $\log_{10}$ copies/mL (SD)	−0.92 (0.10)	−1.33 (0.17)	−1.37 (0.31)	−1.61 (0.26)	−0.01 (0.14)
Pairwise *P* value† vs					
Placebo	<0.001	<0.001	<0.001	<0.001	
BIC 100 mg	<0.001	0.10	0.15		
Mean Δ HIV-1 RNA day 11 from baseline, $\log_{10}$ copies/mL (SD)	−1.45 (0.10)	−2.08 (0.21)	−2.06 (0.35)	−2.43 (0.39)	0.08 (0.30)
Pairwise *P* value† vs					
Placebo	<0.001	<0.001	<0.001	<0.001	
BIC 100 mg	<0.001	0.11	0.09		
Mean max reduction from baseline HIV-1 RNA, $\log_{10}$ copies/mL (SD)	−1.52 (0.08)	−2.18 (0.24)	−2.31 (0.19)	−2.91 (0.53)	−0.12 (0.18)
Pairwise *P* value† vs					
Placebo	<0.001	<0.001	<0.001	<0.001	
BIC 100 mg	<0.001	0.004	0.01		
Participants achieving HIV-1 RNA <50 copies/mL by end of study, n (%)	0	0	1 (25)	2 (50)	0
Mean viral decay slope (SD)	−0.18 (0.01)	−0.25 (0.03)	−0.27 (0.06)	−0.32 (0.04)	−0.01 (0.02)

*One patient was excluded from virologic assessments as HIV-1 RNA on day 1 was 173 copies/mL.
†2-sided *t* test.

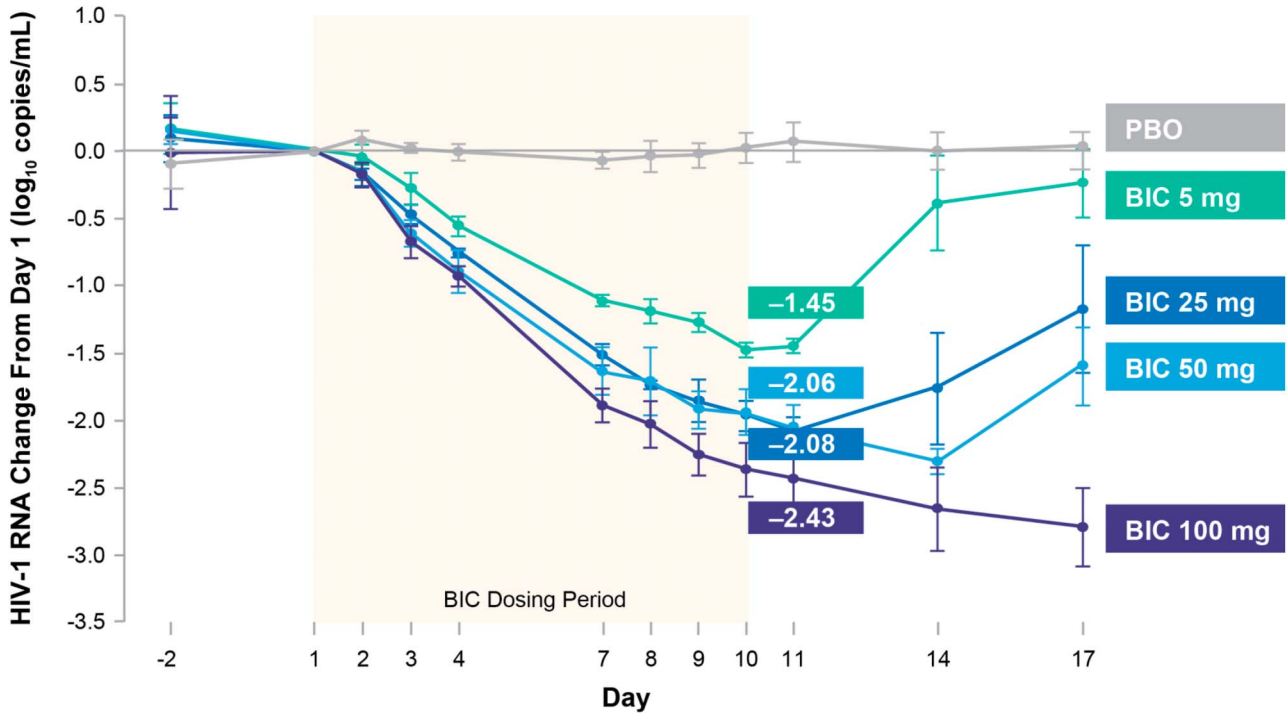

FIGURE 2. Mean change (95% CI) in HIV-1 RNA. PBO = placebo.

resistance-associated substitutions emerged during this study through day 17. At day 11, phenotypic susceptibility data to BIC were available for 10 of the 16 participant isolates, and there were no significant changes in susceptibility to BIC from baseline (median 0.91-fold change; range 0.60- to 1.15-fold change).

Safety

Through 10 days of monotherapy, BIC was well tolerated. The most frequently occurring treatment-emergent AEs in any dose group in 2 or more subjects were diarrhea (BIC 5 and 100 mg, n = 1 each) and headache (BIC 5, 25, 100 mg, and placebo, n = 1 each). The remaining AEs occurred in only 1 subject receiving study treatment. Two participants who received BIC (5 and 100 mg) had a drug-related AE (diarrhea, grade 1); no other drug-related AE occurred in this study. All reported AEs were mild or moderate, and there were no serious AEs. No subject stopped study medication for safety or tolerability reasons, and no deaths occurred. No notable changes in laboratory results or vital signs were observed, and all ECG results were reported as either normal or not clinically significant.

DISCUSSION

In this phase 1b, dose-ranging monotherapy study, treatment with 10 days of BIC led to rapid decreases in HIV-1

TABLE 3. Bictegravir Steady-State Pharmacokinetics on Day 10

	BIC Multiple-Dose PK Day 10			
PK Parameter	**5 mg (n = 4)**	**25 mg (n = 4)**	**50 mg (n = 4)**	**100 mg (n = 4)**
AUC_{tau} (ng*h/mL)	9983.0 (26.7)	48,950.3 (40.0)	87,538.4 (32.7)	178,901.7 (17.8)
AR_AUC (%)	160.2 (16.1)	157.4 (38.0)	125.3 (16.7)	193.3 (11.6)
C_{tau} (ng/mL)	225.3 (37.5)	1052.3 (54.1)	2053.0 (47.6)	4520.0 (21.9)
C_{max} (ng/mL)	741.5 (18.2)	3475.0 (20.5)	6080.0 (21.8)	12,235.0 (24.9)
AR_C_{max} (%)	149.8 (4.4)	138.5 (27.0)	122.0 (10.9)	168.4 (9.6)
T_{max} (h)	1.5 (0.8, 3.0)	1.3 (1.0, 1.5)	1.8 (1.3, 2.5)	2.7 (1.3, 4.0)
T_{last} (h)	168.0 (145.0, 168.7)	111.1 (99.0, 145.0)	169.2 (168.8, 169.5)	169.8 (157.0, 170.1)
$t_{1/2}$ (h)	20.8 (17.2, 23.8)	15.9 (14.1, 19.4)	17.8 (15.5, 20.5)	20.9 (17.9, 24.5)
CL_{ss}/F (mL/h)	523.8 (22.0)	567.3 (34.7)	621.9 (34.0)	570.6 (15.3)
V_z/F (mL)	15,526.6 (38.9)	13,231.5 (32.4)	15,559.1 (20.3)	17,620.6 (31.7)

Data are presented as mean (% CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).
Accumulation ratio of AUC (AR_AUC) = AUC_{tau} on day 10/AUC_{0-24} on day 1; Accumulation ratio of C_{max} (AR_C_{max}) = C_{max} on day 10/C_{max} on day 1.

RNA from baseline that were sustained throughout treatment without viral breakthrough. The decrease in HIV-1 RNA demonstrated a dose–response relationship, and there was a delay in post-treatment viral rebound in the 50-mg and 100-mg dose groups. Three participants (1 in the 50 mg arm and 2 in the 100 mg arm) achieved virologic suppression (<50 copies/mL) by the end of this short-term study.

No primary INSTI resistance mutations were selected during 10 days of monotherapy and through day 17. Bictegravir was safe and well tolerated at all dose levels. BIC demonstrated rapid absorption in the dose range tested, and the steady-state plasma exposure was approximately dose-proportional up to a 100 mg dose in HIV-infected participants. The accumulation ratios were consistent with its terminal half-life, indicating time-independent pharmacokinetics, and its half-life is supportive of once-daily therapy without the need for a PK booster. The mean trough concentrations observed were above the in vitro protein-adjusted concentration that results in 95% inhibition (162 ng/mL) at all dose levels studied.

BIC is a promising once-daily unboosted INSTI that showed potent antiviral activity in this 10-day proof-of-concept study. Given these results, it is being evaluated in a phase 2 study with the fixed-dose combination of 200 mg emtricitabine (FTC) and 25 mg tenofovir alafenamide (TAF),[14] and in phase 3 studies as a single-tablet regimen of BIC/FTC/TAF. This combination was shown to have synergy in in vitro virologic studies.[11] Coformulation of BIC with FTC and TAF into a single-tablet regimen provides a potent novel unboosted INSTI-based regimen with an expanded in vitro resistance profile that can be administered once daily and offers potential advantages over existing INSTI-containing regimens.

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