

Pharmacokinetic and Clinical Data Supporting the LEN Reloading Strategy for BIC/LEN Single-Tablet Regimen Dosing in the ARTISTRY Studies

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Conclusions

- Pharmacokinetic (PK) data indicate that overall lenacapavir (LEN) concentrations remain above the inhibitory quotient (IQ)1 threshold even with 7 consecutive missed daily doses of bictegrovir 75 mg/lenacapavir 50 mg (BIC/LEN) single-tablet regimen (STR)
 - LEN reloading with 600 mg on Days 1 and 2 after reinitiating BIC/LEN is not needed with ≤ 7 consecutive days of missed doses; however, with > 7 days of missed doses, LEN reloading is recommended to quickly re-establish near steady-state exposures
- Clinical data from participants in the ARTISTRY studies who missed > 7 doses of BIC/LEN and received LEN reloading demonstrated sustained viral suppression
- Collectively, PK and clinical evidence supports the LEN reloading strategy as implemented in the ARTISTRY studies following > 7 days of consecutive missed BIC/LEN doses when restarting BIC/LEN daily dosing

Plain Language Summary

- BIC/LEN is an HIV treatment that combines two medicines, bictegrovir (BIC) and lenacapavir (LEN), into a single tablet taken once a day
- In the ARTISTRY-1 and ARTISTRY-2 studies, BIC/LEN was safe and worked well for people with HIV
- During these studies, participants received extra doses of LEN on Days 1 and 2, in addition to their daily BIC/LEN treatment. This was done to raise drug levels in the body to get to target levels more quickly
 - If participants missed more than 7 days of BIC/LEN in a row, they needed to restart treatment and receive the extra LEN doses again on Days 1 and 2
- Researchers measured the amount of LEN in participants' bodies during these and other studies. They also used mathematical models to predict drug levels after different numbers of missed BIC/LEN doses
- Researchers also looked at how well BIC/LEN controlled HIV in participants who missed more than 7 days of treatment and received the extra LEN doses when they restarted BIC/LEN
- Based on the predicted drug levels and results from participants who restarted treatment with the extra LEN doses, BIC/LEN continued to work well in controlling HIV

Introduction

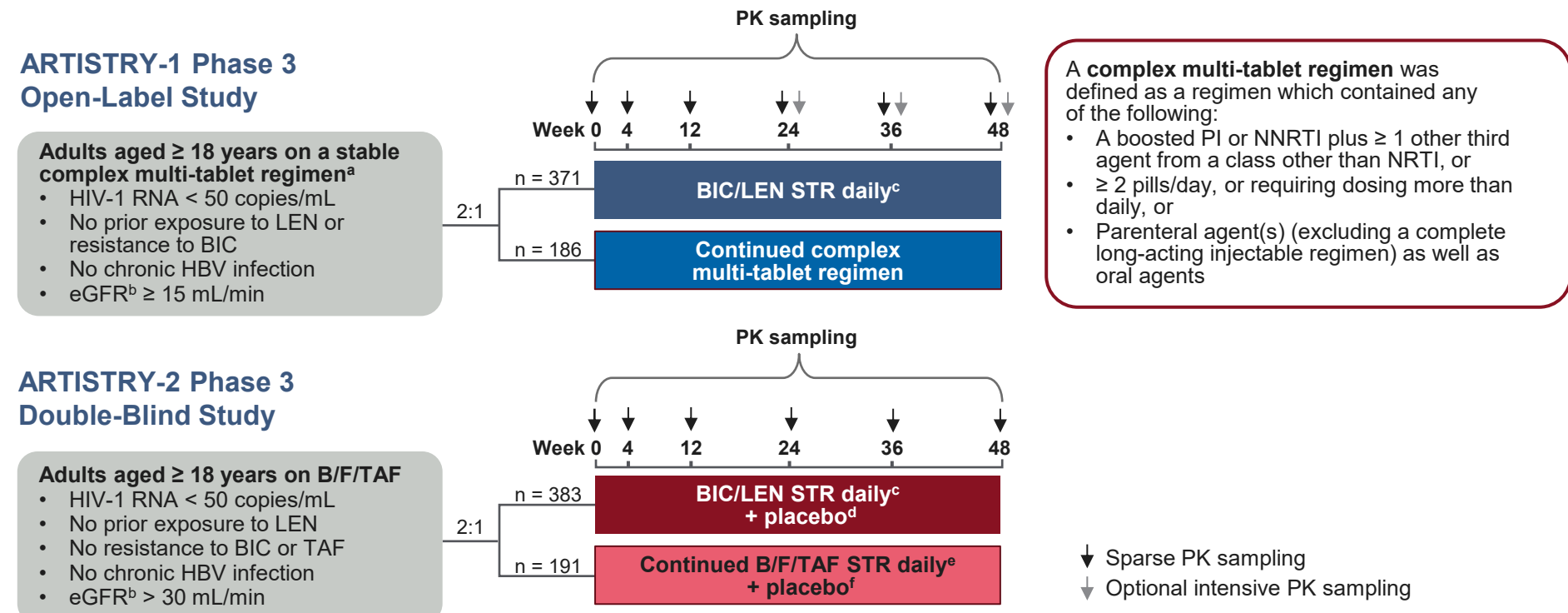
- Oral BIC/LEN is approved by the US Food and Drug Administration as a STR for the treatment of HIV-1¹
- BIC/LEN taken once daily, initiated with loading doses of oral LEN 600 mg on Days 1 and 2, demonstrated safety and efficacy in virologically suppressed people with HIV-1 in the ARTISTRY-1 and -2 studies (**Figure 1**)^{2,3}
 - LEN loading doses on Days 1 and 2 quickly achieve therapeutic levels of LEN
- BIC does not require loading to achieve therapeutic exposures quickly
 - While the plasma elimination half-life of BIC ranges from approximately 19 to 21 hours, its antiviral efficacy is also influenced by the prolonged residence time in the integrase binding pocket (approximately 163 hours [6.8 days]), providing additional pharmacologic coverage during periods of missed dosing^{1,4}
- In the ARTISTRY studies, participants who missed > 7 days of consecutive BIC/LEN doses restarted BIC/LEN with reloading doses of oral LEN 600 mg on Days 1 and 2 of treatment reinitiation as per the protocol
 - Dosing and reloading instructions are consistent with prescribing information¹

Objective

- To describe the PK and clinical data supporting the protocol-defined BIC/LEN dosing and LEN reloading recommendations in the ARTISTRY studies, including reloading with > 7 consecutive days of missed BIC/LEN doses

Methods

Figure 1. Design of ARTISTRY-1 and ARTISTRY-2 Studies



^aDue to ARV resistance, intolerance, drug-drug interactions, or contraindication to existing STRs. ^bAccording to the Cockcroft-Gault formula for creatinine clearance. ^cBIC/LEN 75/50 mg; with oral loading dose of LEN 600 mg on Days 1 and 2 of treatment. ^dPlacebo-to-match B/F/TAF. ^eParticipants received placebo-to-match oral LEN on Days 1 and 2 of treatment. Placebo-to-match BIC/LEN. ARV, antiretroviral; B or BIC, bictegrovir; eGFR, estimated glomerular filtration rate; F, emtricitabine; HBV, hepatitis B virus; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetic; STR, single-tablet regimen; TAF, tenofovir alafenamide.

PK Sampling Schema

- Sparse PK samples were collected from all participants on BIC/LEN in both studies at the following timepoints:
 - Day 1 at predose and 4 hours post-dose
 - ARTISTRY-1: Weeks 4, 12, 24, 36, 48 at trough and 2 hours post-dose
 - ARTISTRY-2: Weeks 4, 12, 24, 36, 48 at trough and Weeks 24 and 36 at 2 hours post-dose
- An intensive PK (iPK) substudy was performed in a subset of participants in the BIC/LEN group of ARTISTRY-1 at a steady-state visit at either Week 24, 36, or 48
 - Blood samples were collected at trough, and 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose
- Plasma concentrations of BIC/LEN were determined using validated bioanalytical assays

Population PK Analysis

- A population PK model was developed to characterize LEN PK as a component of BIC/LEN
 - Data from 11 studies were used, including single-dose studies as well as the ARTISTRY-1 and -2 studies
 - A full fixed-effect covariate model was used to estimate the effects of relevant covariates (body weight, sex, Japanese ethnicity, food effect, kidney function) on LEN PK
 - Ten thousand virtual individuals were generated, and stochastic simulation was performed at steady state to assess LEN exposure following up to 7 days of missed BIC/LEN daily maintenance doses

Clinical Data

- The clinical occurrence of LEN reloading, after > 7 days of missed BIC/LEN doses per protocol, across both studies and the virologic outcomes for those participants at Week 48 were evaluated

Results

Table 1. Demographics and Baseline Characteristics

	ARTISTRY-1 n = 371	ARTISTRY-2 n = 383	Participants Contributing to the PopPK Model n = 1295
Age, years, median (range)	60 (22-84)	47 (23-77)	49 (18-84)
Male sex at birth, n (%)	307 (83)	314 (82)	996 (77)
Race, n (%)			
White	260 (70)	199 (52)	777 (60)
Black or African American	64 (17)	113 (30)	335 (26)
Asian	16 (4)	51 (13)	118 (9)
Other	12 (3)	20 (5)	46 (4)
Missing	19 (5)	0	19 (2)
Ethnicity, n (%)			
Hispanic or Latinx	80 (22)	106 (28)	439 (34)
Japanese	Not available	Not available	31 (2)
Weight, kg, median (range)	79.6 (43.5-156)	81.1 (49.6-159)	78.0 (43.5-164)
BMI, kg/m ² , median (range)	26.1 (16.6-55.0)	26.8 (16.8-52.9)	NA
CrCl, mL/min, median (range)	82.9 (24.6-200)	101 (39.3-307)	102 (24.6-330)
Fed status, n (%)			
Fasted	—	—	272 (21)
Fed	—	—	156 (12)
Unknown	371 (100)	383 (100)	857 (66)
Missing	—	—	10 (1)
HIV status, n (%)			
No HIV	0	0	333 (26)
Virologically suppressed	358 (96)	376 (98)	857 (66)
Treatment naïve	0	0	105 (8)

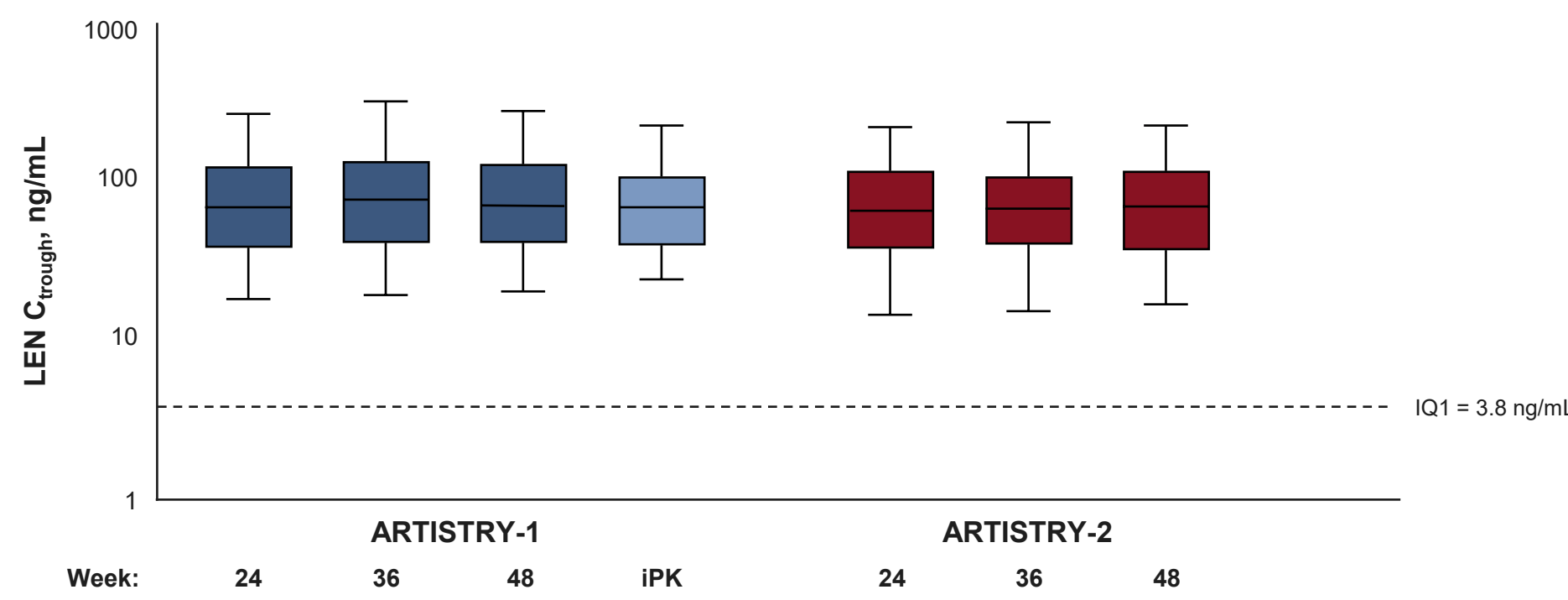
BMI, body mass index; CrCl, creatinine clearance; NA, not available; PopPK, population pharmacokinetics.

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Results (cont.)

- Observed mean trough plasma drug concentration (C_{trough}) values in the ARTISTRY studies were 21- to 30-fold above the IQ1 threshold (3.8 ng/mL) for LEN (**Figure 2**)

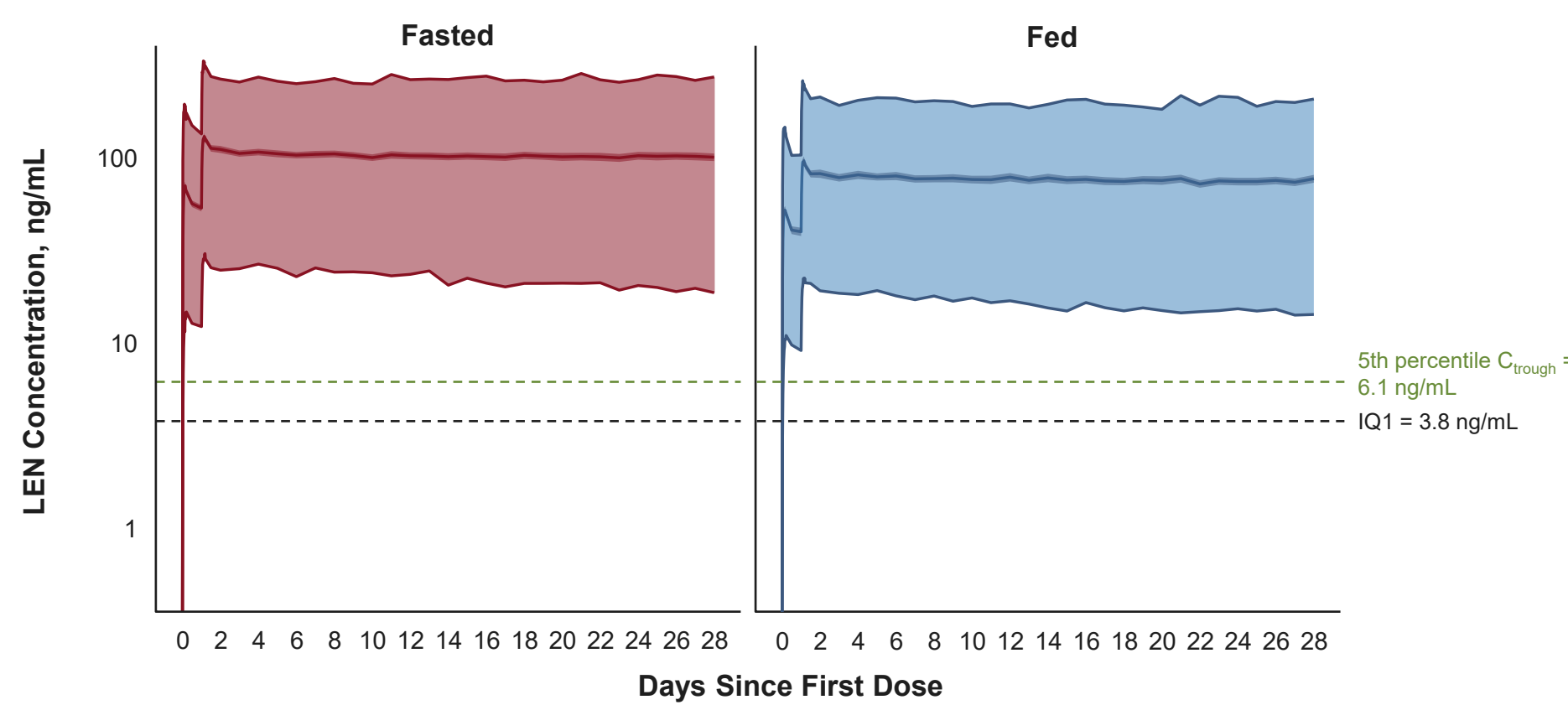
Figure 2. Plasma LEN C_{trough} Values From ARTISTRY-1 and ARTISTRY-2 Observed at Steady State



Box plots depict median (horizontal line), interquartile range (box), and 5th-95th percentiles (whiskers). C_{trough} , trough plasma drug concentration; iPK, intensive PK; IQ, inhibitory quotient; LEN, lenacapavir.

- After initiation of daily BIC/LEN with LEN loading doses on Days 1 and 2, plasma LEN concentrations quickly increase and remain above IQ1 (3.8 ng/mL) and the simulated population 5th percentile of C_{trough} obtained 26 weeks after subcutaneous LEN administration in treatment-naïve people with HIV (6.1 ng/mL) (**Figure 3**)

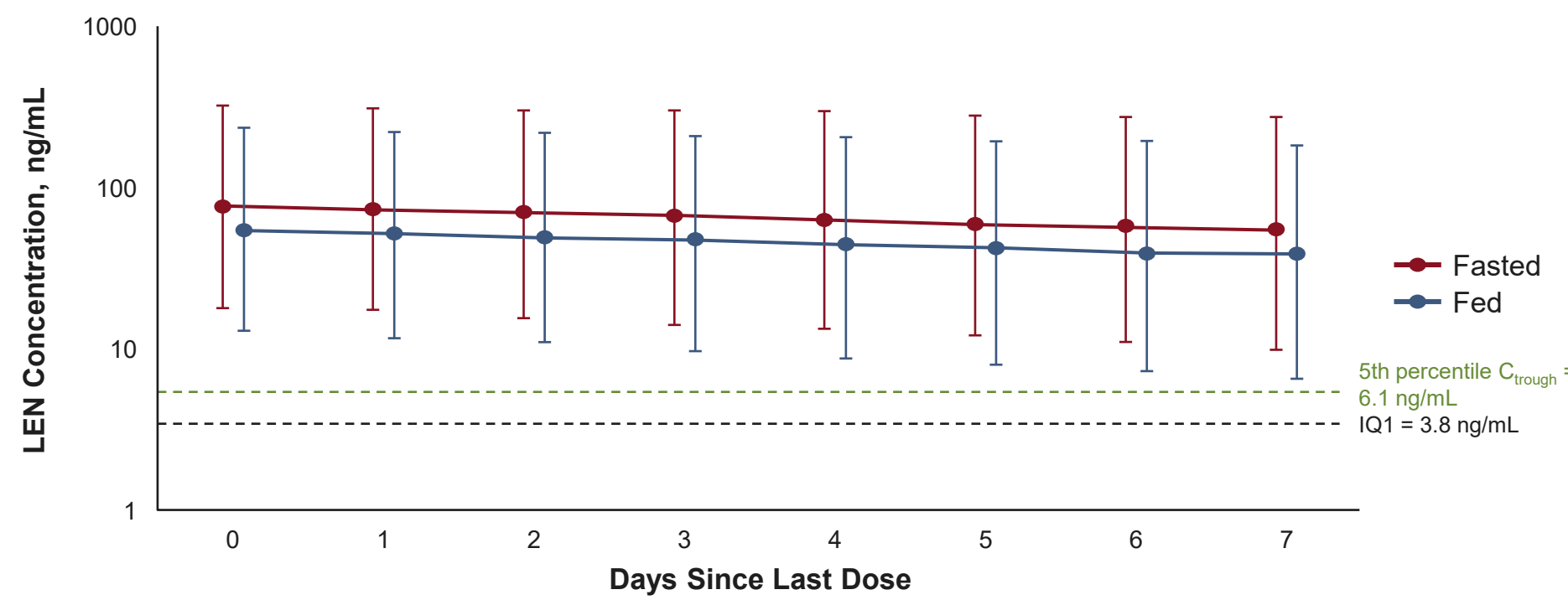
Figure 3. Plasma LEN Concentrations Following Daily BIC/LEN Dosing With LEN Loading Doses Administered on Days 1 and 2



Central solid lines are the means, with the shaded area around the mean line corresponding to the 90% CI of the mean. Lower and upper lines of the outer shaded area correspond to the 5th and 95th percentiles of the population prediction interval. Green dashed line corresponds to simulated population 5th percentile of C_{trough} obtained 26 weeks after subcutaneous LEN administration in treatment-naïve people with HIV (6.1 ng/mL). Black dashed line corresponds to IQ1 (3.8 ng/mL). BIC, bictegrovir; CI, confidence interval; C_{trough} , trough plasma drug concentration; IQ, inhibitory quotient; LEN, lenacapavir.

- After 7 days of consecutively missed BIC/LEN doses, simulation results showed a median (90% prediction interval) LEN C_{trough} of 55.1 (9.86, 273) ng/mL (fasted) and 38.9 (6.49, 183) ng/mL (fed), exceeding the IQ1 of 3.8 ng/mL for LEN (**Figure 4, Table 2**)

Figure 4. Projected Median (90% PI) LEN Concentrations After Missed BIC/LEN Doses



Red and blue data points and corresponding error bars have been slightly staggered at each timepoint for clarity. Line markers are median values and error bars are 90% PI. Green dashed line corresponds to simulated population 5th percentile of C_{trough} obtained 26 weeks after subcutaneous LEN administration in treatment-naïve people with HIV (6.1 ng/mL). Black dashed line corresponds to IQ1 (3.8 ng/mL). BIC, bictegrovir; C_{trough} , trough plasma drug concentration; IQ, inhibitory quotient; LEN, lenacapavir; PI, prediction interval.

Disclosures: PA, AS, PS, DDM, and CJ are employees of, and own stocks/shares in, Gilead Sciences, Inc.

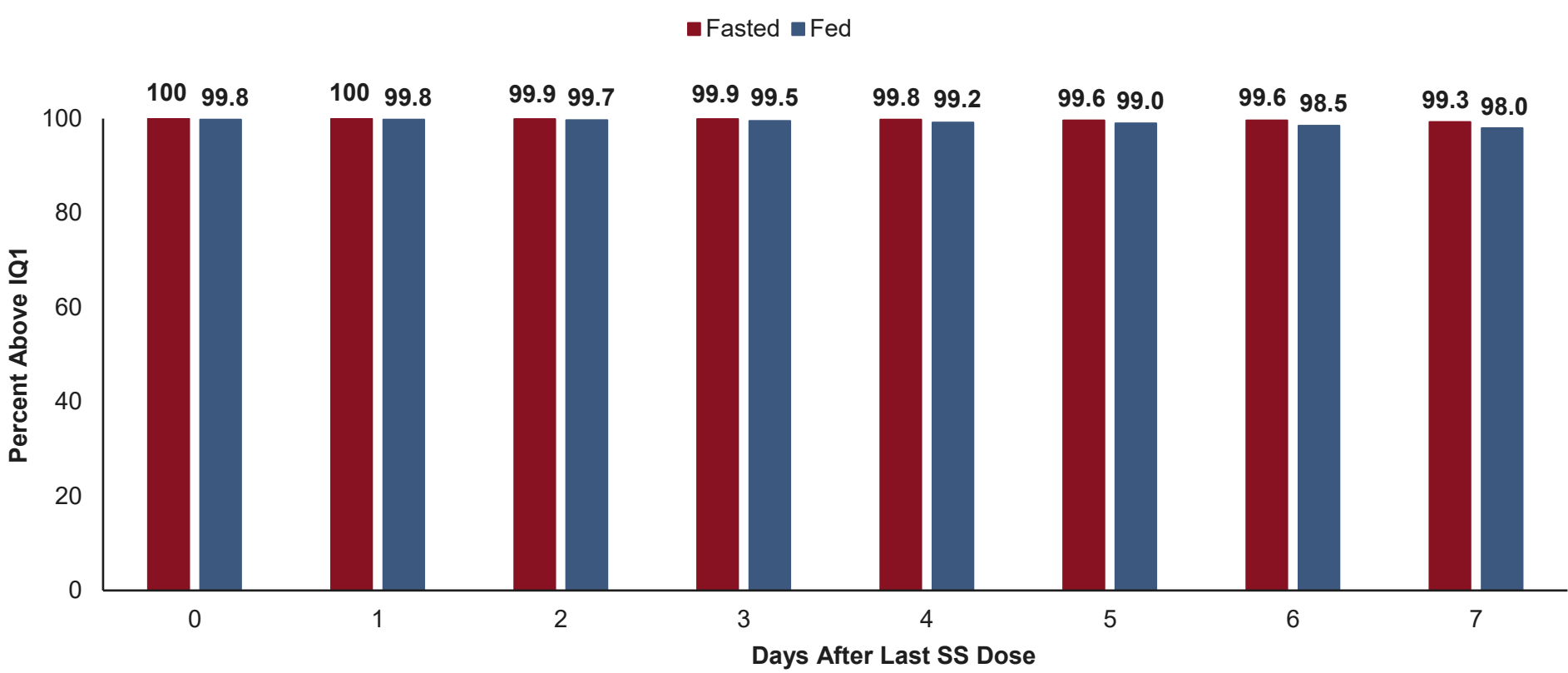
Table 2. Projected Median (90% PI) LEN Concentrations After Missed BIC/LEN Doses

Days After Last SS BIC/LEN Dose	Median (90% PI) LEN Concentration, ng/mL		Mean (90% CI) LEN Concentration, ng/mL	
	Fasted	Fed	Fasted	Fed
0	77.4 (18.0, 324)	55.4 (13.0, 236)	113 (110, 115)	80.5 (78.4, 82.5)
1	72.7 (17.5, 310)	52.4 (11.7, 221)	109 (106, 111)	76.8 (74.9, 78.6)
2	70.2 (15.5, 301)	48.9 (11.0, 219)	104 (101, 107)	74.4 (72.4, 76.3)
3	66.8 (14.1, 301)	48.1 (9.67, 209)	101 (97.9, 103)	70.9 (69.0, 72.7)
4	63.6 (13.3, 298)	44.8 (8.77, 205)	96.2 (93.7, 98.7)	67.9 (66.1, 69.7)
5	59.4 (12.1, 280)	42.3 (8.04, 193)	92.4 (89.9, 94.9)	65.3 (63.5, 67.0)
6	57.1 (11.0, 273)	39.9 (7.29, 194)	89.7 (87.2, 92.1)	62.5 (60.8, 64.1)
7	55.1 (9.86, 273)	38.9 (6.49, 183)	86.4 (84.0, 88.8)	61.1 (59.3, 62.8)

BIC, bictegrovir; CI, confidence interval; LEN, lenacapavir; PI, prediction interval; SS, steady state.

- Most participants had projected LEN concentrations above IQ1 up to 7 days after the last steady-state dose of BIC/LEN (**Figure 5**)

Figure 5. Percentage of People on BIC/LEN With Projected LEN Plasma Concentrations Above IQ1



IQ1 = 3.8 ng/mL. BIC, bictegrovir; IQ, inhibitory quotient; LEN, lenacapavir; SS, steady state.

- Most participants had projected LEN concentrations above the simulated population 5th percentile of C_{trough} obtained 26 weeks after subcutaneous LEN administration in treatment-naïve people with HIV for up to 7 days after the last steady-state dose of BIC/LEN
 - In studies using subcutaneous LEN, there was robust efficacy at concentrations above the population 5th percentile of C_{trough}
- Seven participants from both studies missed > 7 consecutive doses and underwent LEN reloading with BIC/LEN reinitiation per the protocol
- All seven participants had continued suppression of HIV-1 RNA at Week 48, at last available measure, or at measure after reloading (**Table 3**)

Table 3. Clinical Data From BIC/LEN Participants Receiving LEN Reloading (After Missing > 7 Consecutive Daily Doses) During the ARTISTRY Studies

Participant	Study	Study Days of LEN Reloading	HIV-1 RNA at Reloading	HIV-1 RNA at Week 48	Study Drug Discontinued?
1	ARTISTRY-1	258 and 259 439 and 440 ^a	None detected None detected	< 20 copies/mL	No
2	ARTISTRY-1	176 and 177	Not conducted	None detected	No
3	ARTISTRY-1	153 and 154	Not conducted	None detected	No
4	ARTISTRY-2	43 and 44	None detected	None detected	Yes ^b
5	ARTISTRY-2	54 and 55	Not conducted	None detected	No
6	ARTISTRY-2	111 and 112	None detected	No virologic data ^c	Yes ^c
7	ARTISTRY-2	343 and 344 ^d	Not conducted	< 20 copies/mL	No

^aThe second reloading occurred after Week 48. Subsequent HIV-1 RNA at Week 72 (Study Day 502) was not detected. ^bDiscontinued study drug due to participant decision. ^cDiscontinued study drug due to investigator's discretion prior to Week 48; last available HIV-1 RNA at Week 24 (Study Day 174) was not detected. ^dReloading occurred after Week 48. Subsequent HIV-1 RNA at Week 60 (Study Day 427) remained < 20 copies/mL. BIC, bictegrovir; LEN, lenacapavir.