Pharmacokinetic Analysis of Oral Once-Daily Bictegravir (BIC) Plus Lenacapavir (LEN) Administered Separately (BIC 75 mg + LEN 25 mg; BIC 75 mg + LEN 50 mg) and as BIC/LEN 75/50 mg Single Tablet Regimen to Support Phase 3 Dose Selection

P049

ARTISTRY-1, GS-US-621-6292

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Conclusions

- Steady-state exposures of BIC and LEN in the Phase 2 portion of ARTISTRY-1 were consistent with historical data associated with efficacy and safety
  - Similar BIC exposures and dose linear increases in LEN exposures for BIC 75 mg + LEN 25 mg versus BIC 75 mg + LEN 50 mg were observed
- BIC/LEN 75/50 mg STR (dosed with or without food) was projected to have comparable exposures for each component, compared with single agents coadministered
- Overall, based on the totality of data from the Phase 2 portion of ARTISTRY-1 and the rBA study, the BIC/LEN 75/50 mg STR is being utilized in the Phase 3 ARTISTRY-1[1] and ARTISTRY-2 studies[2]
  - This dose is expected to provide reasonable operating characteristics with respect to considerations of PK, efficacy, and safety
  - It may afford better coverage for efficacious exposures in the setting of LEN interindividual variability and any potential for missed doses with a chronic QD regimen

Plain Language Summary

- BIC + LEN is a treatment for human immunodeficiency virus (HIV), in which the medicines bictegravir (BIC) and lenacapavir (LEN) are taken together once a day
- BIC + LEN may be another treatment option for people who are taking more than one pill or other single-tablet HIV treatments or drug treatments
- The ARTISTRY-1 study showed that BIC + LEN is safe and effective in people with HIV
- Information from ARTISTRY-1 and another study was used to see how BIC and LEN move into, through, and out of the body (pharmacokinetics)
- BIC and LEN were given in two different ways:
  - As two separate pills with the same dose of BIC (75 mg) and either a lower (25 mg) or higher (50 mg) dose of LEN
  - As a combined pill (single tablet) with a higher dose of LEN (BIC/LEN 75 mg/50 mg)
- The results predicted that:
  - The higher dose of LEN (50 mg) will stay at effective levels in the body for a longer time than the lower dose of LEN (25 mg)
  - Levels of both BIC and LEN in the body will be similar when taken as a combined tablet compared with when taken as separate tablets
  - Taking BIC and LEN as a combined tablet with or without food will not significantly affect levels in the body
- The combined tablet of BIC and LEN (75/50 mg) is being studied further in two Phase 3 studies

Introduction

- Single tablet regimens (STRs) are the global standard for HIV treatment[3]
- An STR of bictegravir (BIC) and lenacapavir (LEN) is being developed that could optimize treatment in virologically suppressed people with HIV (PWH) who are not eligible for currently available STRs
  - BIC is a global guideline-recommended integrase strand transfer inhibitor with a high barrier to resistance[3-6]
  - LEN is a first-in-class capsid inhibitor with no documented *de novo* resistance in the absence of prior exposure[7]
- Coadministration of BIC + LEN has been investigated in the Phase 2 portion of the ARTISTRY-1 trial
  - BIC + LEN demonstrated efficacy and safety in virologically suppressed PWH
- Here we report pharmacokinetic (PK) data for BIC and LEN, either given as single agents coadministered or as an STR

Objective

- To inform dose selection for Phase 3 by analyzing PK data from:
  - The Phase 2 portion of ARTISTRY-1 (BIC + LEN as single agents coadministered)
  - A relative bioavailability study (rBA; BIC + LEN as single agents vs BIC/LEN as STR)
  - Population pharmacokinetics (popPK) modeling of cumulative LEN data

Methods

Scan the QR code for the LEN PopPK model structure

- We report PK data from:
  - The Phase 2 portion of ARTISTRY-1 (NCT05502341), an ongoing, randomized, open-label, multicenter Phase 2/3 study
    - PK evaluation of two dose combinations of BIC + LEN (BIC 75 mg + LEN 25 mg or BIC 75 mg + LEN 50 mg) coadministered once daily (QD) for 24 weeks
  - A Phase 1, open-label, parallel, multicenter rBA study (GS-US-621-6292)
    - PK evaluation of single doses of BIC/LEN (75/50 mg) as STR and BIC 75 mg + LEN 25 mg as single agents coadministered

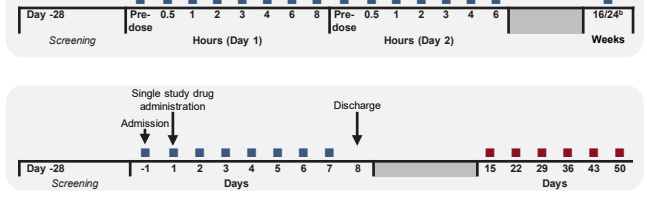
Dosing and PK Sampling Schedules

Phase 2 Portion of ARTISTRY-1

- Adults aged ≥ 18 years
- HIV-1 RNA < 50 copies/mL on stable baseline regimen for ≥ 6 months before screening
- eGFR ≥ 15 mL/min; not on renal replacement therapy

rBA Study

- Male PWH aged 18-45 years
- BMI of ≥ 19.0 and ≤ 30.0 kg/m^2
- Normal renal function (CrCl ≥ 90 mL/min)[a]



In the Phase 2 portion of ARTISTRY-1, BIC + LEN were dosed daily; intensive PK sampling was performed under fasted conditions on Days 1 and 2 and at Weeks 16 or 24; on all other days, BIC and LEN were given without regard to food. In the rBA study, PK samples were collected predose and until Day 8 (BIC) and Day 50 (LEN) following single dose of BIC and LEN.
[a]Cockcroft-Gault equation. [b]Participants continued daily dosing; PK samples were taken pre-dose, and 0.5-, 1-, 2-, 3-, 4-, 6- and 8-hours post-dose.
BIC, bictegravir; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; LEN, lenacapavir; PK, pharmacokinetic; PWH, people with HIV; rBA, relative bioavailability.

- PK parameters (maximum observed plasma drug concentration [C_{max}], trough plasma concentration [C_{trough}], area under the plasma concentration–time curve over the dosing interval [AUC_{tau}], area under the curve to infinity [AUC_{inf}], and time to reach maximum drug concentration [T_{max}], as applicable) derived by noncompartmental analysis were compared using descriptive statistics
- For LEN, a popPK model was developed with pooled LEN studies to further enable LEN dose selection
  - The developed model reasonably described the PK of 25 and 50 mg QD maintenance dosing of LEN in combination with BIC in a Phase 2 study in PWH and reproduced the observed interindividual variability for LEN in population simulations
  - For further information, popPK model specifications have been presented at the American Conference on Pharmacometrics[8]

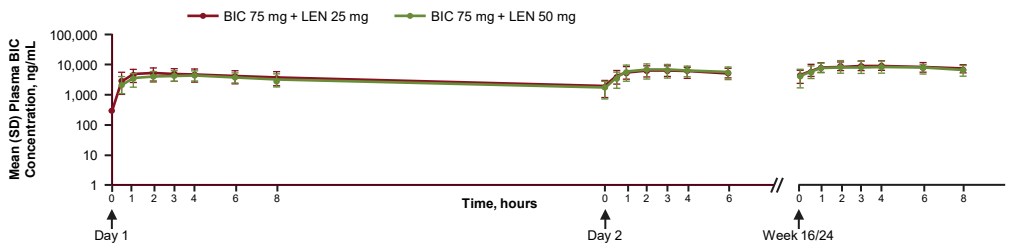
Results

Baseline Demographics

	Phase 2 Portion of ARTISTRY-1[a,b]		Relative Bioavailability Study		
	BIC 75 mg + LEN 25 mg (n = 34)	BIC 75 mg + LEN 50 mg (n = 34)	BIC 75 mg + LEN 25 mg (n = 60, fasted)	BIC/LEN 75/50 mg STR (n = 60, fasted)	BIC/LEN 75/50 mg STR (n = 30, high-fat meal)
Age, years, median (range)	62 (26-74)	61 (34-74)	33 (27-38)	27 (24-37)	30 (27-36)
Male sex at birth, n (%)	27 (79)	28 (82)	23 (38)	33 (55)	16 (53)
Race, n (%)					
White	20 (59)	20 (59)	30 (50)	44 (73)	13 (43)
Black	12 (35)	14 (41)	25 (42)	10 (17)	7 (23)
Asian	0	0	4 (7)	1 (2)	9 (30)
American Indian or Alaska Native	0	0	1 (2)	0	0
Other	2 (6)	0	0	5 (8)	1 (3)
Weight, kg, median (Q1, Q3)	83 (72, 92)	82 (73, 93)	76 (65, 81)	72 (65, 82)	71 (65, 79)
BMI, kg/m^2, median (Q1, Q3)	27 (23, 31)	27 (23, 32)	27 (25, 28)	26 (23, 28)	25 (22, 26)

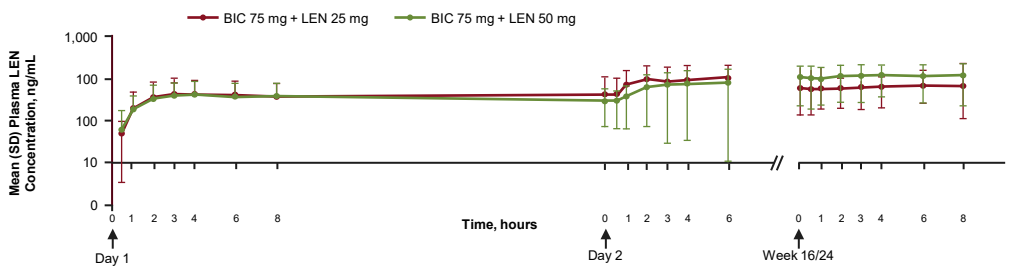
[a]BIC and LEN were administered in conjunction with loading doses of oral LEN 600 mg on Days 1 and 2.
[b]Intensive PK sampling (Days 1 and 2 and Weeks 16 or 24) was performed under fasted conditions; on all other days, BIC and LEN were given without regard to food.
BIC, bictegravir; LEN, lenacapavir; PK, pharmacokinetic; Q, quartile; STR, single tablet regimen.

BIC Plasma Concentration Versus Time Profiles in the Phase 2 Portion of ARTISTRY-1



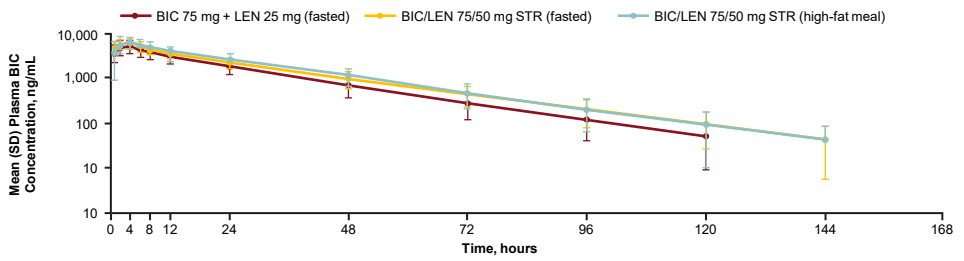
Values below the limit of quantification were treated as 0; where data points have no negative error bars, the value is negative and therefore not visualized on a log scale.
BIC, bictegravir; LEN, lenacapavir.

LEN Plasma Concentration Versus Time Profiles in the Phase 2 Portion of ARTISTRY-1



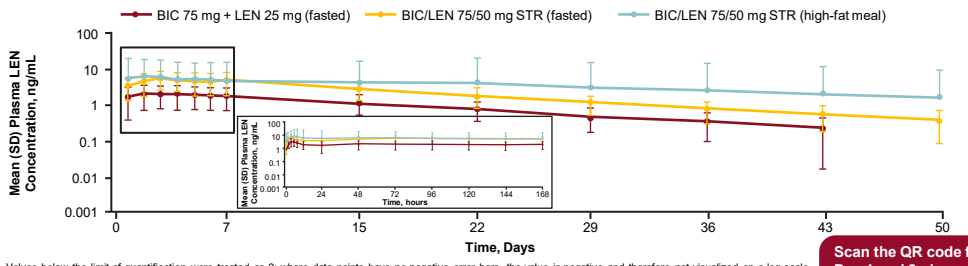
Values below the limit of quantification were treated as 0; where data points have no negative error bars, the value is negative and therefore not visualized on a log scale.
BIC, bictegravir; LEN, lenacapavir.

BIC Plasma Concentration Versus Time Profiles in the rBA Study



Values below the limit of quantification were treated as 0; where data points have no negative error bars, the value is negative and therefore not visualized on a log scale.
BIC, bictegravir; LEN, lenacapavir; rBA, relative bioavailability; STR, single tablet regimen.

LEN Plasma Concentration Versus Time Profiles in the rBA Study



Values below the limit of quantification were treated as 0; where data points have no negative error bars, the value is negative and therefore not visualized on a log scale.
BIC, bictegravir; LEN, lenacapavir; rBA, relative bioavailability; STR, single tablet regimen.

Scan the QR code for Day 1 and 2 plasma PK parameters in the Phase 2 portion of ARTISTRY-1

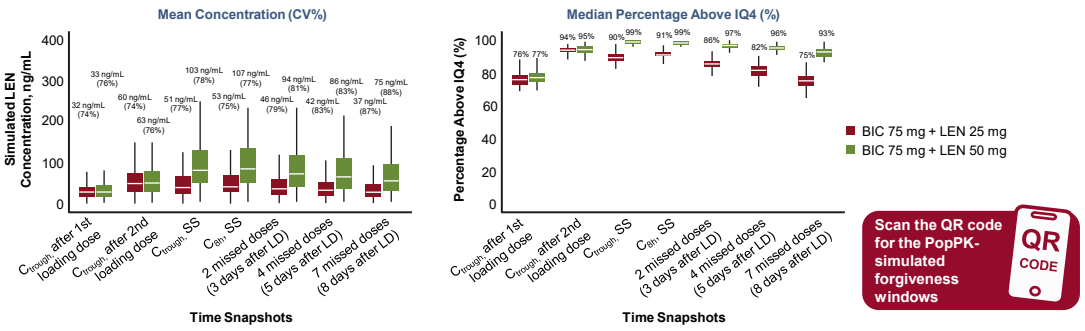
Plasma PK Parameters

		Phase 2 Portion of ARTISTRY-1 (n = 47; steady-state data from Weeks 16 or 24 [daily dosing])[a,b]		Relative Bioavailability Study (n = 150; collected until Day 8 [BIC] and Day 50 [LEN] after a single dose)				
		BIC 75 mg + LEN 25 mg (n = 26)	BIC 75 mg + LEN 50 mg (n = 21)	BIC 75 mg + LEN 25 mg (n = 60, fasted)	BIC/LEN 75/50 mg STR (n = 60, fasted)	%GLSM Ratio (90% CI) BIC/LEN 75/50 mg STR vs BIC 75 mg + LEN 25 mg (fasted)	BIC/LEN 75/50 mg STR (n = 30; high-fat meal)	%GLSM Ratio (90% CI) BIC/LEN 75/50 mg STR (high-fat meal vs fasted)
C_{max}, ng/mL, mean (%CV)	BIC	9740 (31)	9460 (37)	5790 (29)	6580 (22)	117 (107, 128)	7580 (20)	116 (107, 126)
	LEN	82 (100)	134 (74)	3.7 (58)	7.4 (61)	200 (169, 236)	9.4 (212)	86 (67, 109)
C_{trough}, ng/mL, mean (%CV)	BIC	4330 (47)	4540 (64)	–	–	–	–	–
	LEN	58 (77)	108 (80)	–	–	–	–	–
AUC_{tau}, h*ng/mL, mean (%CV)	BIC	150,000 (31)	137,000 (44)	–	–	–	–	–
	LEN	1460 (77)	2690 (79)	–	–	–	–	–
AUC_{inf}, h*ng/mL, mean (%CV)	BIC	–	–	129,000 (34)	160,000 (28)	127 (114, 142)	178,000 (26)	112 (101, 125)
	LEN	–	–	1120 (57)	2570 (50)[c]	237 (202, 278)	5570 (357)[d]	78 (59, 102)[e]
T_{max}, h, median (Q1, Q3)	BIC	3.0 (2.0, 4.0)	2.0 (1.0, 3.0)	2.0 (2.0, 4.0)	2.0 (1.5, 4.0)	–	2.0 (2.0, 4.0)	–
	LEN	6.0 (4.0, 8.0)	4.0 (3.0, 6.0)	4.0 (4.0, 6.0)	4.0 (4.0, 4.0)	–	4.0 (4.0, 8.0)	–

[a]BIC and LEN were administered in conjunction with loading doses of oral LEN 600 mg on Days 1 and 2. [b]Intensive PK sampling was performed under fasted conditions (Days 1 and 2 and Weeks 16 or 24); on all other days, BIC and LEN were given without regard to food. [c]Without outlier data, AUC_{inf} (%CV) was 2580 (50). [d]Without outlier data, AUC_{inf} (%CV) was 1940 (71). [e]Without outlier data, %GLSM ratio (90% CI) was 67 (53, 83).
%CV, percent coefficient of variation; %GLSM, percent geometric least squares mean; AUC_{tau}, area under the plasma concentration–time curve over the dosing interval; AUC_{inf}, area under the curve to infinity; BIC, bictegravir; C_{max}, maximum observed plasma drug concentration; C_{trough}, trough plasma concentration; LEN, lenacapavir; PK, pharmacokinetic; Q, quartile; STR, single tablet regimen; T_{max}, time to reach maximum drug concentration.

- BIC exposures were comparable between BIC + LEN doses in the Phase 2 portion of ARTISTRY-1 and were within the predefined bounds for STR versus single agents coadministered in the rBA study
- Dose linear increases were observed in steady-state LEN exposures for coadministered BIC 75 mg + LEN 50 mg versus BIC 75 mg + LEN 25 mg in the Phase 2 portion of ARTISTRY-1, and for single doses of BIC/LEN 75/50 mg STR versus coadministered BIC 75 mg + LEN 25 mg in the rBA study
- The high-fat meal led to a minor reduction in LEN exposure versus fasted conditions in the BIC/LEN 75/50 mg STR group, which was not considered clinically relevant based on the functional therapeutic window and exposure margins projected for LEN at the corresponding dose

PopPK-Generated Simulation of LEN Exposures at Steady State Following Once-Daily Administration of LEN 25 or 50 mg Combined with BIC



Horizontal lines indicate median, the box ends indicate Q1 and Q3, and the vertical lines indicate the minimum and maximum values. Simulations were performed with 100 subjects and 100 replicates. The boxplots show the respective variability for the projections within each treatment group at the snapshot timepoints.
BIC, bictegravir; C_{trough}, trough plasma concentration; CV%, percent coefficient of variation; C_{8h}, plasma drug concentration 8 hours after administration; IQ4, inhibitory quotient 4; LD, last dose; LEN, lenacapavir; PopPK, population pharmacokinetics; Q, quartile; SS, steady state.

Scan the QR code for the PopPK-simulated forgiveness windows

- Simulation results suggested that 50 mg LEN QD would provide better coverage for C_{trough} than 25 mg
  - This was based on comparison between corresponding exposures and percentage of participants above the IQ4 threshold at various time snapshots, including missed dose scenarios

References: **1.** NCT05502341. https://clinicaltrials.gov/study/NCT05502341 (accessed Sep. 19, 2024). **2.** NCT06333808. https://clinicaltrials.gov/study/NCT06333808 (accessed Sep. 19, 2024). **3.** DHHS. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf (accessed Aug. 14, 2024). **4.** EACS. https://www.eacsociety.org/media/guidelines-12.0.pdf (accessed Aug. 14, 2024). **5.** Acosta RK, et al. *Antimicrob Agents Chemother*. 2019;63:e02533-18. **6.** Gandhi RT, et al. *JAMA*. 2023;329:63-84. **7.** Dvory-Sobol H, et al. *Curr Opin HIV AIDS*. 2022;17:15-21. **8.** Oh E, et al. Poster W-089 presented at: ACoP; November 10-13, 2024; Phoenix, AZ.

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