Bictegravir/Lenacapavir: Baseline and Week 48 Resistance in the ARTISTRY-2 Trial

P048

ARTISTRY-2 (GS-US-621-6290)

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Conclusions

- In ARTISTRY-2, bictegravir/lenacapavir (BIC/LEN) single-tablet regimen (STR) maintained high levels of efficacy at Week 48 regardless of pre-existing resistance-associated mutations (RAMs)
  - Participants with and without baseline primary RAMs, including integrase strand-transfer inhibitor (INSTI) RAMs, showed similarly high rates of virologic suppression (VS)
- The development of RAMs was rare, occurring in 1/383 (0.3%) participants receiving BIC/LEN
- These data support the use of a BIC/LEN STR as a promising treatment option for virologically suppressed people with HIV

Plain Language Summary

- In the ongoing ARTISTRY-2 study, bictegravir/lenacapavir (BIC/LEN) controlled human immunodeficiency virus (HIV) as effectively as bictegravir/emtricitabine/tenofovir alafenamide
- Researchers wanted to understand whether genetic changes (mutations) in HIV affected how well BIC/LEN controlled HIV. They also wanted to know whether new mutations developed while people were taking BIC/LEN
- At the start of the study, some people had mutations in their HIV, but this did not affect how well BIC/LEN worked
- Over 48 weeks, only one of the 383 people who took BIC/LEN in the study developed a mutation in their HIV
  - BIC/LEN still worked against HIV with this mutation in laboratory tests

Introduction

- STRs are a global guideline-recommended standard-of-care treatment for HIV[1,2]
  - Novel STRs could expand treatment options for those for whom current STRs are unsuitable due to antiretroviral resistance, intolerance, drug-drug interactions, or contraindications[1,3-5]
- ARTISTRY-2 (NCT06333808) is an ongoing Phase 3 trial in people with HIV with VS, evaluating the safety and efficacy of switching to a BIC/LEN STR compared with continuing standard-of-care treatment with B/F/TAF
  - BIC is a guideline-recommended INSTI[1,2,6]
  - LEN is a first-in-class capsid inhibitor[7]
- At Week 48, BIC/LEN was shown to be generally well tolerated and was noninferior to B/F/TAF in maintaining high levels of VS in ARTISTRY-2[8]

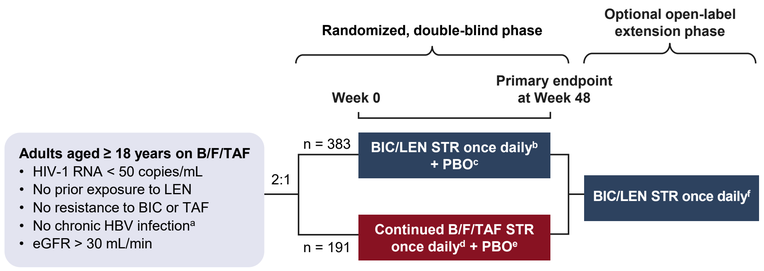
Objective

- To report HIV-1 resistance analyses in the Phase 3 ARTISTRY-2 study at baseline and through 48 weeks of treatment

Methods

- ARTISTRY-2 is a Phase 3, randomized, double-blind, active-controlled, multicenter trial

Figure 1. Phase 3 ARTISTRY-2 Study Design



Endpoints:
- **Primary:**
  - HIV-1 RNA ≥ 50 copies/mL (US FDA Snapshot algorithm; 4% noninferiority margin) at Week 48
- **Secondary:**
  - HIV-1 RNA < 50 copies/mL (US FDA Snapshot algorithm) at Week 48
  - Change from baseline in CD4 cell count at Week 48
  - Treatment-emergent AEs through Week 48
- **Additional:**
  - Virology analyses at baseline through Week 48

[a]Determined by the following at the screening visit: either positive HBV surface antigen and negative HBV surface antibody regardless of HBV core antibody status, or positive HBV core antibody and negative HBV surface antibody regardless of HBV surface antigen status.
[b]BIC/LEN 75/50 mg; participants received an oral loading dose of LEN 600 mg on Days 1 and 2 of treatment.
[c]Placebo-to-match B/F/TAF.
[d]B/F/TAF 50/200/25 mg; participants received placebo-to-match LEN on Days 1 and 2 of treatment.
[e]Placebo-to-match BIC/LEN.
[f]BIC/LEN 75/50 mg; participants who received B/F/TAF in the randomized phase received an oral loading dose of LEN 600 mg on Days 1 and 2 of initiating BIC/LEN in the extension phase.
AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BIC, bictegravir; CD4, cluster of differentiation 4; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; HBV, hepatitis B virus; LEN, lenacapavir; PBO, placebo; STR, single-tablet regimen; TAF, tenofovir alafenamide.

- Pre-existing RAMs in reverse transcriptase (RT), protease (PR), and IN were characterized using historical genotypic reports, if available, and retrospective proviral DNA genotyping of baseline whole blood samples (GenoSure Archive; Monogram Biosciences, San Francisco, CA, USA)[a]
- Post-baseline resistance analysis (RT, PR, IN, and capsid; Monogram Biosciences or Institute of Immunology and Genetics, Kaiserslautern, Germany) was performed for participants who experienced virologic failure (VF) with HIV-1 RNA ≥ 200 copies/mL (resistance analysis population [RAP])
  - VF was defined as:
    - Confirmed virologic rebound: HIV-1 RNA ≥ 50 copies/mL, subsequently confirmed at next visit
    - Or last visit with HIV-1 RNA ≥ 50 copies/mL
- Participants with VF who resuppressed by Week 48 were not included in the final RAP

[a]DeepType HIV (Institute of Immunology and Genetics) was used for some participants for whom GenoSure Archive data were unavailable.

Table 1. Primary RAMs Analyzed

	Mutation[9-11]
NRTI	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R in RT
NNRTI	L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C/L, M230L/I in RT
PI	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L/V, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M in PR
INSTI	T66I/A/K, E92Q/G/V, G118R, F121C/Y, G140R, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K in IN
CAI	L56I, M66I, Q67H/K/N, K70H/N/S/R, N74D/S, A105S/T, T107A/C/N/S in CA

CA, capsid; CAI, capsid inhibitor; IN, integrase; INSTI, integrase strand-transfer inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PR, protease; RAM, resistance-associated mutation; RT, reverse transcriptase.

Results

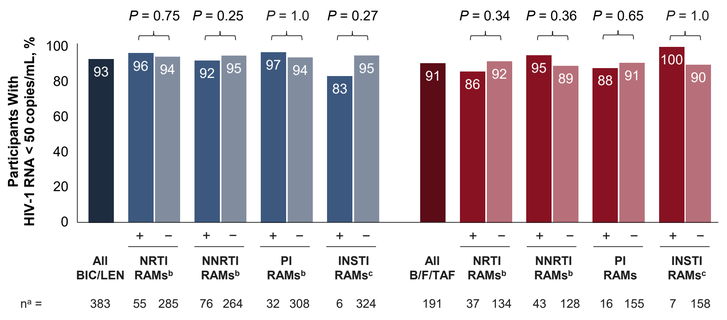
Table 2. Pre-existing NRTI, NNRTI, PI, and INSTI RAMs[a]

	BIC/LEN n = 383	B/F/TAF n = 191	All N = 574[b]
Participants with PR/RT data, n	340	171	511
Primary NRTI RAMs, n (%)	55 (16.2)	37 (21.6)	92 (18.0)
Any TAM[c]	30 (8.8)	18 (10.5)	48 (9.4)
M184I/V	35 (10.3)	24 (14.0)	59 (11.5)
L74I/V	3 (0.9)	6 (3.5)	9 (1.8)
K65E/N/R	3 (0.9)	1 (0.6)	4 (0.8)
Y115F	2 (0.6)	2 (1.2)	4 (0.8)
K70E	2 (0.6)	0	2 (0.4)
Primary NNRTI RAMs,[c] n (%)	76 (22.4)	43 (25.1)	119 (23.3)
K103N/S	32 (9.4)	21 (12.3)	53 (10.4)
E138A/G/K/Q/R	21 (6.2)	9 (5.3)	30 (5.9)
Primary PI RAMs,[d] n (%)	32 (9.4)	16 (9.4)	48 (9.4)
M46I/L	16 (4.7)	13 (7.6)	29 (5.7)
Participants with IN data, n	330	165	495
Primary INSTI RAMs, n (%)	6 (1.8)	7 (4.2)	13 (2.6)
T66A/I/K	1 (0.3)	1 (0.6)	2 (0.4)
E92G/Q/V	1 (0.3)	4 (2.4)	5 (1.0)
G140R	1 (0.3)	0	1 (0.2)
Y143C/H/R	1 (0.3)	1 (0.6)	2 (0.4)
Q148H/K/R	2 (0.6)	1 (0.6)	3 (0.6)

[a]Some participants who experienced virologic failure may have had capsid genotyping done on baseline samples (DeepType HIV; Institute of Immunology and Genetics).
[b]Participants who received at least one dose of study drug (full analysis set).
[c]TAMs are M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R.
[d]For NNRTIs and PIs, only individual RAMs that are documented in more than 5% of participants are shown.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BIC/LEN, bictegravir/lenacapavir; IN, integrase; INSTI, integrase strand-transfer inhibitor; RAM, resistance-associated mutation; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PR, protease; RT, reverse transcriptase; TAM, thymidine analog mutation.

- Overall, the most prevalent RAMs detected were M184I/V (11.5%) and K103N/S (10.4%) in RT
  - Of the 59 participants with M184V/I, 26 had additional nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) RAMs or thymidine analog mutations

Figure 2. Week 48 Virologic Outcomes per Baseline RAM Category (US FDA Snapshot Algorithm)



P values calculated using the Fisher exact test. + and – symbols indicate the group of participants with and without RAMs at baseline, respectively.
[a]Number of participants with available viral load data.
[b]Protease and reverse transcriptase genotypic data were available for 374/383 and 188/191 participants in the BIC/LEN and B/F/TAF groups, respectively.
[c]Integrase genotypic data were available for 330/383 and 165/191 participants in the BIC/LEN and B/F/TAF groups, respectively.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BIC/LEN, bictegravir/lenacapavir; FDA, Food and Drug Administration; INSTI, integrase strand-transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation.

- There were high VS rates across all groups
- Presence of baseline RAMs did not affect BIC/LEN or B/F/TAF efficacy at Week 48

Final RAP

- Of the 574 participants in the full analysis set, four (BIC/LEN: n = 2; B/F/TAF: n = 2) met the criteria for post-baseline resistance testing and were included in the Week 48 final RAP

Table 3. Final RAP

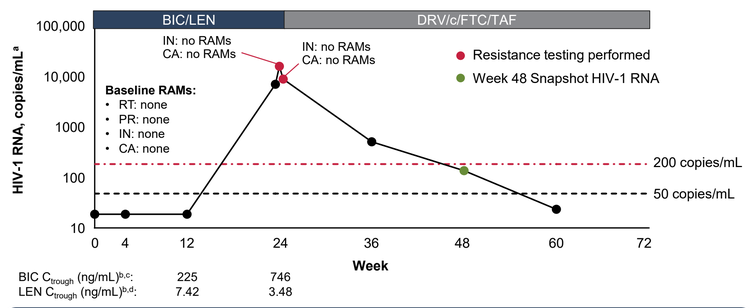
Resistance Categories	BIC/LEN n = 383	B/F/TAF n = 191	All N = 574[a]
Final RAP, n (%)	2 (0.5)	2 (1.0)	4 (0.7)
With data, n (%)	1 (0.3)	0	1 (0.2)
NRTI RAMs	0	0	0
NNRTI RAMs	0	0	0
PI RAMs	0	0	0
INSTI RAMs	1 (0.3)	0	1 (0.2)
CAI RAMs	0	0	0

[a]Participants who received at least one dose of study drug (full analysis set).
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BIC/LEN, bictegravir/lenacapavir; CAI, capsid; INSTI, integrase strand-transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation; RAP, resistance analysis population.

- The development of RAMs was rare, occurring in 1/383 (0.3%) participants receiving BIC/LEN[8]
  - R263K in IN was detected at Week 36 in one participant in the BIC/LEN group who had prior exposure to INSTIs (dolutegravir and raltegravir)
  - Phenotypic susceptibility to BIC was maintained (half maximal effective concentration [EC_{50}] fold-change from wild-type: 2.0; biological cutoff: 3.5-10)
  - No capsid RAMs were detected

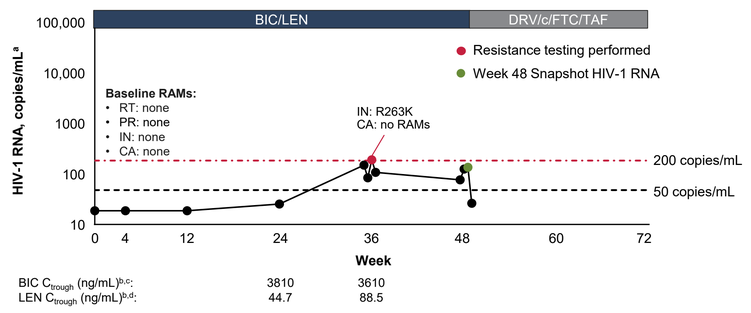
Figure 3. Details of Participants in the Final RAP

Participant 1 (On BIC/LEN STR)



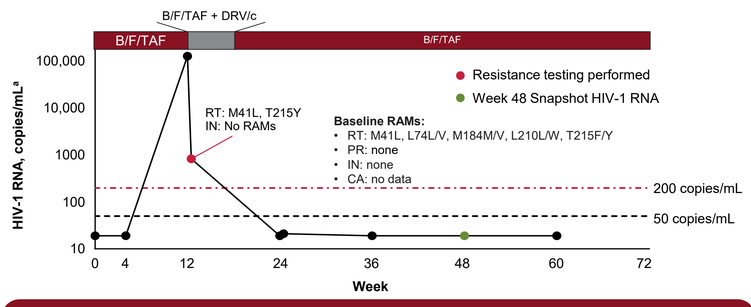
- No genotypic resistance in IN or CA detected at VF (phenotypic resistance data are unavailable)
- Resuppression after switch to DRV/c/FTC/TAF and at last visit on study drug
- Observed BIC C_{trough} was 1.4-fold and 4.6-fold higher than BIC IQ1[e] at Weeks 12 and 24, respectively
- Observed LEN C_{trough} was 1.9-fold higher and 1.1-fold lower than LEN IQ1[e] at Weeks 12 and 24, respectively

Participant 2 (On BIC/LEN STR)



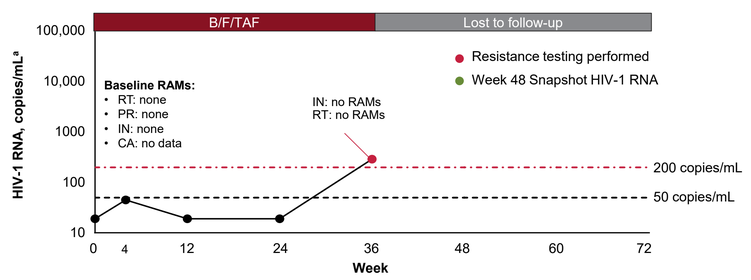
- R236K in IN at VF
  - Full phenotypic susceptibility to BIC (EC_{50} fold-change from WT: 2.0; biological cutoff: 3.5-10)
  - Previous exposure to DTG and RAL
- No resistance in capsid detected
- Resuppression after switch to DRV/c/FTC/TAF
- Observed BIC C_{trough} was 23.5- and 22.3-fold higher than BIC IQ1[e] at Weeks 24 and 36, respectively
- Observed LEN C_{trough} was 11.6- and 22.9-fold higher than LEN IQ1[e] at Weeks 24 and 36, respectively

Participant 3 (On B/F/TAF STR)



- NRTI resistance (M41L and T215Y) detected at both baseline and VF (not considered treatment emergent)
  - Full phenotypic sensitivity to FTC at Week 12 (EC_{50} fold-change from WT: 2.2; biological cutoff: 3.5)
  - Partial phenotypic sensitivity to TFV at Week 12 (EC_{50} fold-change from WT: 1.5; clinical cutoff: 1.4-4)
- Resuppression after switch to B/F/TAF + DRV/c
  - Participant later switched back to B/F/TAF and maintained suppression

Participant 4 (On B/F/TAF STR)



- No genotypic resistance in IN or RT and no phenotypic resistance to study drugs detected at VF
- Participant lost to follow-up

Pharmacokinetic data are unavailable for participants in the B/F/TAF group.
[a]LLOQ for the HIV-1 RNA assay was 20 copies/mL; values < 20 copies/mL are presented as 19 copies/mL.
[b]C_{trough} data are presented for the visit at which VF was identified and the preceding visit only.
[c]LLOQ for the BIC pharmacokinetic assay was 20 ng/mL.
[d]LLOQ for the LEN pharmacokinetic assay was 0.5 ng/mL.
[e]The IQ1 is the threshold above which efficacious exposure against HIV is expected (BIC IQ1: 162 ng/mL; LEN IQ1: 3.87 ng/mL).
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BIC, bictegravir; c, cobicistat; CA, capsid; C_{trough}, trough concentration; DRV, darunavir; DTG, dolutegravir; EC_{50}, effective concentration of half maximal response; FTC, emtricitabine; IN, integrase; IQ, inhibitory quotient; LEN, lenacapavir; LLOQ, lower limit of quantitation; NRTI, nucleoside/nucleotide reverse transcriptase; PR, protease; RAL, raltegravir; RAM, resistance-associated mutation; RAP, resistance analysis population; RT, reverse transcriptase; STR, single-tablet regimen; TAF, tenofovir alafenamide; TFV, tenofovir; VF, virologic failure; WT, wild-type.

References: **1.** Department of Health and Human Services. https://clinicalinfo.hiv.gov/sites/g/files/mnhszr391/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf (accessed Sept. 29, 2026). **2.** European AIDS Clinical Society. https://eacs.sanfordguide.com/en/eacs-hiv/art/eacs-initial-regimens-arv-naive-adults (accessed Aug. 19, 2026). **3.** Chang H-M, et al. *BMC Infect Dis*. 2022;22:2. **4.** Rolle C-P, et al. *J Virus Erad*. 2020;6:100021. **5.** Amariles P, et al. *Pharmaceutics*. 2023;15:2488. **6.** Gandhi RT, et al. *JAMA*. 2025;333:609-28. **7.** Dvory-Sobol H, et al. *Curr Opin HIV AIDS*. 2022;17:15-21. **8.** Meissner EG, et al. *Lancet HIV*. 2026;13:e538-47. **9.** Wensing AM, et al. *Top Antivir Med*. 2025;33:457-73. **10.** Margot NA, et al. *J Infect Dis*. 2017;215:920-7. **11.** Demirdjian S, et al. *J Med Virol*. 2025;97:e70340.

Acknowledgments: We thank all study participants, investigators, and staff. We thank Mauricio Montezuma and Sarah Puryear (Gilead Sciences, Inc.) for their clinical development support. These studies were funded by Gilead Sciences, Inc. Medical writing support was provided by Lindsay Fawcett, BSc (Aspire Scientific Ltd, UK), and was funded by Gilead Sciences, Inc.

Disclosures: **MLD**, **KA**, **CS**, **PA**, **KM**, **PS**, **NM**, and **CC** are employees of, and own stocks/shares in, Gilead Sciences, Inc. **EGM** reports grants (paid to institution) from ViiV Healthcare and serving as the Independent Data Monitoring Committee Chair for a ViiV Healthcare–funded clinical trial.

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