

Baseline and week 48 resistance analysis in participants receiving bicitegravir + lenacapavir in the phase 2 ARTISTRY-1 study

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Background: ARTISTRY-1 is an operationally seamless Phase 2/3 study evaluating the safety and efficacy of once-daily oral lenacapavir (LEN) + bicitegravir (BIC) in virologically suppressed participants without known integrase strand-transfer inhibitor (INSTI) resistance, compared to a complex multi-tablet regimen.

Methods: Baseline HIV-1 resistance-associated mutations (RAMs) were assessed via historical genotypic reports (HGR) and proviral DNA genotyping (GenoSure Archive, Monogram Biosciences). The impact of baseline RAMs on Week 48 efficacy in the Phase 2 part of the study was evaluated. Post-baseline genotypic and phenotypic resistance was assessed in participants with confirmed virologic rebound (HIV-1 RNA ≥ 50 copies/ml; analyzed if ≥ 200 copies/ml).

Results: Baseline HIV-1 genotypic data from HGR and/or proviral DNA analyses were available for 98% (125/128) of participants. RAMs for nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) were found in 81%, 65%, and 46% of participants, respectively; 11% had primary INSTI RAMs by proviral DNA genotyping. Baseline RAMs had no impact on Week 48 efficacy. One participant with baseline resistance to NRTIs, NNRTIs, and PIs, and detectable baseline viral load met the criteria for resistance testing. A novel capsid polymorphism (N74T) emerged in this individual, with no impact on LEN susceptibility.

Conclusions: Despite high frequencies of baseline resistance, substantial rates of viral suppression were maintained through Week 48 and no on-treatment resistance to study drugs was detected. These findings support the development of once-daily BIC+LEN STR to improve and optimize treatment options in individuals on complex ART.

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Introduction

Once-daily single tablet regimens (STRs) are the standard of care for HIV treatment, offering convenience and improved adherence [1]. However, a subset of people with HIV (PWH) receive complex antiretroviral therapy (ART) regimens due to factors including acquired antiretroviral (ARV) drug resistance, intolerance, toxicity, drug-drug interactions, or contraindications to available STRs [1–3]. A regimen combining bictegravir (BIC), a guideline-recommended integrase strand-transfer inhibitor (INSTI) with a high barrier to resistance [1,4–6], and lenacapavir (LEN), a first-in-class capsid inhibitor (CAI) with an orthogonal resistance profile to existing drug classes [7] and no preexisting resistance [8], may provide a simplified and effective alternative for virologically suppressed (VS) individuals unable to use current STRs.

ARTISTRY-1 is a Phase 2/3 study evaluating the safety and efficacy of a complete regimen of BIC+LEN compared to continuing a complex regimen. In the Phase 2 portion of ARTISTRY-1, VS participants ($n = 128$) receiving complex ART (defined by pill burden and drug class composition) were randomized to receive BIC 75 mg with either LEN 25 mg or LEN 50 mg, or to continue their complex regimen. At baseline, participants were taking an antiretroviral regimen containing between 2 and 9 pills per day with a median duration of HIV treatment of 27.0 (19.9–32.0) years [9]. At Week 48, high rates of virologic suppression were observed across all treatment groups (90.4–100.0%) [9]. The objectives of the current analysis were to characterize the baseline resistance-associated mutation (RAM) profile of all participants and to evaluate the potential emergence of resistance to BIC and/or LEN after 48 weeks of treatment.

Materials and methods

ARTISTRY-1 study

Detailed methods for Study GS-US-621-6289 (NCT05502341) have been described previously [9]. This report focuses on the Phase 2 portion of the study.

Eligible participants were adults (≥ 18 years) receiving a complex antiretroviral therapy (ART) regimen, with documented HIV-1 RNA < 50 copies/ml for at least 6 months prior to screening and at the screening visit, no prior LEN exposure, and no known INSTI RAMs. Participants were randomized in a 2:2:1 ratio to receive once-daily BIC (75 mg) + LEN (25 mg), BIC (75 mg) + LEN (50 mg), or continue their existing regimen [9]. The primary endpoint was assessed at Week 24, after which all participants who elected to continue in the extension period received BIC (75 mg)/LEN (50 mg) fixed-dose combination (FDC).

Resistance analyses

Baseline resistance was evaluated using historical genotypic report (HGR) data entered electronically by the investigators and retrospective proviral DNA genotyping (GenoSure Archive, Monogram Biosciences, South San Francisco) on Day 1. RAMs of interest included mutations associated with nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and INSTIs. The presence of INSTI mutations in HGR was an exclusion criterion for enrollment. In cases where both HGR and proviral genotypic data were available, a composite sequence encompassing all mutations detected was used in the analysis.

Postbaseline resistance testing was performed in participants with confirmed virologic rebound (2 consecutive HIV-1 RNA > 50 copies/ml), with analysis at the confirmed visit if HIV-1 RNA ≥ 200 copies/ml for CA, PR, RT, IN using assays from Monogram Biosciences (South San Francisco, USA; Gag-Pro GeneSeq and PhenoSense, PSGT, GeneSeq and PhenoSense Integrase) or Seq-IT (Kaiserlautern, Germany; DeepTypeHIV [Illumina MiSeq, amplicon based next-generation sequencing HIV-1 *gag-pol*, 2%-variant-frequency-threshold] [10]). The impact of baseline RAMs on treatment response at Week 48 was evaluated using Fisher's exact test.

Phenotypic susceptibility to LEN was also assessed by cloning the *gag*-protease region from clinical samples into the infectious clone pXXLAI [7]. These recombinant viruses were used to infect MT-2 cells (cell viability read-out) [7] or Rev-CEM-Luc/GFP cells (Virongy Biosciences, VA, USA; RevLun assay with reporter gene read-out) [11,12]. Drug susceptibility was quantified by measuring ATP-based luminescence (CellTiterGlo [MT-2 assay] or firefly luciferase luminescence (OneGlo [RevLun assay], Promega, Madison, USA) in the presence of serial dilutions of LEN, allowing determination of the 50% effective concentration (EC_{50}). The EC_{50} fold-change (FC) relative to the wild-type (WT) reference virus XXLAI was calculated to assess resistance.

Results

At baseline, a high prevalence of RAMs was observed among participants across all treatment groups (Table 1). Resistance to NRTIs, NNRTIs and PIs was detected in 81%, 65%, and 46% of participants, respectively, highlighting differences across these ARV drug classes. The most common NRTI mutation was M184V/I (69.6%), followed by thymidine-analog mutations (TAMs; 63.2%). Only 10.4% of participants had M184V/I alone, 43% of participants had more than three TAMs, and 28% had more than four TAMs. Primary INSTI RAMs were identified in 11% of participants at baseline by proviral DNA analysis only,

Table 1. Summary of preexisting reverse transcriptase, protease, and integrase resistance-associated mutations in Study ARTISTRY-1 Phase 2.

Resistance-associated mutations	Number of participants with composite baseline PR/RT data, n (%)			
	BIC 75 mg + LEN 25 mg (n = 51)	BIC 75 mg + LEN 50 mg (n = 52)	Complex ART (n = 25)	All (N = 128)
<i>Participants with data (PR/RT)</i>	50 (98.0%)	52 (100%)	23 (92%)	125 (97.7%)
Primary NRTI-RAMs ^a	43 (86.0%)	39 (75.0%)	19 (82.6%)	101 (80.8%)
Average NRTI-RAMs	3.8	4.1	3.0	3.8
TAMs	35 (70.0%)	31 (59.6%)	13 (56.5%)	79 (63.2%)
≥3 TAMs	26 (52.0%)	22 (42.3%)	6 (26.1%)	54 (43.2%)
≥4 TAMs	16 (32.0%)	17 (32.7%)	2 (8.7%)	35 (28.0%)
M184I/V	36 (72.0%)	35 (67.3%)	16 (69.6%)	87 (69.6%)
M184I/V alone	5 (9.8%)	5 (9.6%)	3 (13.0%)	13 (10.4%)
Primary NNRTI-RAMs ^b	30 (60.0%)	34 (65.4%)	17 (73.9%)	81 (64.8%)
Average NNRTI-RAMs	2.4	2.2	2.2	2.2
K103N/S	17 (34.0%)	18 (34.6%)	13 (56.5%)	48 (38.4%)
Y181C/I/V	12 (24.0%)	11 (21.2%)	5 (21.7%)	28 (22.4%)
Primary PI-RAMs ^c	22 (44.0%)	21 (40.4%)	14 (60.9%)	57 (45.6%)
Average PI-RAMs	3.4	3.6	3.0	3.4
M46I/L	11 (22.0%)	17 (32.7%)	6 (26.1%)	34 (27.2%)
L90M	14 (28.0%)	13 (25.0%)	13 (56.5%)	40 (32.0%)
Number of Participants with Proviral DNA Genotypic Baseline IN Data				
<i>Participants with data (IN)^d</i>	35 (68.6%)	39 (75.0%)	20 (80.0%)	94 (73.4%)
Primary INSTI-RAMs ^e	9 (25.7%)	0	1 (5.0%)	10 (10.6%)
Average INSTI-RAMs	1.4	0	1.0	1.4
T66A/I/K	2 (5.7%)	0	0	2 (2.1%)
E92G/Q/V	1 (2.9%)	0	0	1 (1.1%)
G140R	1 (2.9%)	0	0	1 (1.1%)
S147G	1 (2.9%)	0	0	1 (1.1%)
Q148H/K/R	3 (8.6%)	0	1 (5.0%)	4 (4.3%)
N155H/S	4 (11.4%)	0	0	4 (4.3%)
R263K	1 (2.9%)	0	0	1 (1.1%)

^aNRTI RAMs: M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R in RT.

^bNNRTI RAMs: 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.

^cPI RAMs: 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.

^dProviral DNA analysis only (n with data = 94). For all three other mutation categories, n with data = 125.

^eINSTI RAMs: T66I/A/K, E92Q/G/V, G118R, F121C/Y, G140R, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K in IN.

ART, antiretroviral therapy; BIC, bictegravir; FDA, Food and Drug Administration; IN, integrase; INSTI, integrase strand transfer inhibitor; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PR, protease; RAM, resistance-associated mutation; RT, reverse transcriptase.

as the presence of INSTI resistance in HGR was exclusionary and included T66T/A/I/K ($n = 2$, 2.1%), E92E/G/Q/V ($n = 1$, 1.1%), G140G/R ($n = 1$, 1.1%), S147S/G ($n = 1$, 1.1%), Q148Q/H/K/R ($n = 4$, 4.3%), N155N/H/S ($n = 4$, 4.3%), and R263R/K ($n = 1$, 1.1%) (Table S1, Supplementary Digital Content, <http://links.lww.com/QAD/D835>). All participants had HIV-1 subtype B, except for one participant who had HIV-1 subtype C. Despite this high burden of baseline resistance, including INSTI RAMs, virologic suppression at Week 48 was maintained across all study groups with no impact of baseline RAMs on treatment outcomes [13].

Out of the 128 participants enrolled and dosed in the study, three had HIV-RNA ≥ 50 copies/ml at Week 48. Two of these individuals (BIC 75 mg + LEN 25 mg treatment group) had low-level viremia that did not meet the threshold for resistance testing (50 and 98 copies/ml, respectively), and resuppressed without a change in ART at their next visit. The third participant (BIC 75 mg + LEN 50 mg treatment

group; HIV-1 subtype B) experienced confirmed virologic rebound with an HIV-1 RNA of 305 copies/ml at Week 48 (Fig. 1a). This participant had a history of extensive ART exposure and documented resistance to NRTIs, NNRTIs, and PIs. Although VS at screening, HIV-1 RNA was detectable at baseline (90 copies/ml). Prior to study entry, the participant was receiving a complex regimen of boosted darunavir (DRV/r) twice daily, dolutegravir (DTG) twice daily, and maraviroc (MVC) once daily. Resistance testing revealed no emergent INSTI RAMs; however, a novel capsid substitution N74T, was identified by the DeepTypeHIV assay. Following virologic rebound, the participant switched to a regimen of DTG BID+MVC BID, and subcutaneous LEN at the investigator's discretion with resulting viral suppression.

Phenotypic characterization of the emergent N74T capsid substitution was conducted using the laboratory strain HIV-1 XXLAI and SDM to introduce the mutation into the strain and three clinical isolates with diverse polymorphisms in gag

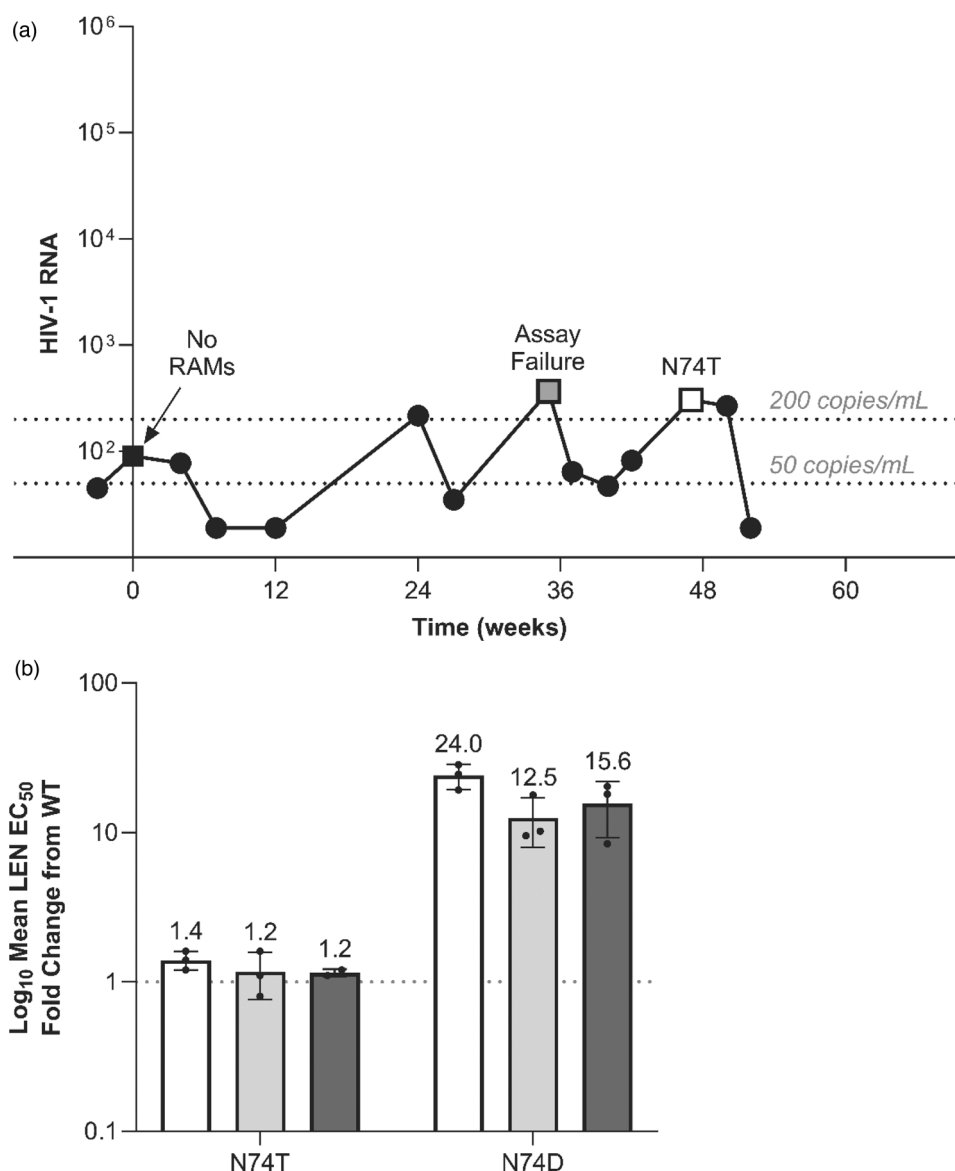


Fig. 1. LEN EC₅₀ fold change of N74T and N74D capsid mutations. (a) The HIV-1 RNA viral load profile of the participant receiving BIC 75 mg + LEN 50mg who experienced viral rebound is shown. At Week 48, the novel N74T polymorphism in capsid was detected (highlighted by a white square). Genotypic analysis at Baseline did not unveil CA resistance-associated mutations (black square). Analysis of the Week 36 visit resulted in assay failure (gray square). (b) LEN susceptibility was tested in three phenotypic assays: the multi-cycle MT-2 assay (white), the multi-cycle RevLun assay (light gray), and the single-cycle PhenoSense Gag-Pro assay (dark gray). LEN FC of each individual experiment was normalized relative to the WT control (dotted gray line; XXLAI for multi-cycle assays, or drug sensitive reference strain [CNDO] containing PR and RT sequences from HIV-1 strain NL4-3 for single-cycle assay). The mean $\pm$ standard deviation was plotted (derived from three independent biological replicates). BIC, bicitgravir; FC, fold change; LEN, lenacapavir; PR, protease; RAM, resistance-associated mutation; RT, reverse transcriptase; WT, wild type.

and no CA RAMs. These engineered viruses were evaluated in single-cycle (Monogram Biosciences) and multi-cycle phenotypic MT-2 and RevLun cellular assays [7,11]. Although the N74T SDM in the XXLAI strain did not replicate, all 3 clinical isolates engineered to express the N74T variant demonstrated minimal changes in LEN susceptibility across all assays, with a mean EC₅₀ FC of 1.4 (MT-2 assay), 1.2 (RevLun assay), and 1.1 (PhenoSenseGT assay) relative to wild-type virus (Fig. 1b). In contrast, the N74D mutant used as a comparator and positive control for

LEN resistance, showed substantial reductions in LEN susceptibility, with FCs of 24.0, 12.5, and 14.1, respectively (Fig. 1b). Additionally, no change in susceptibility to BIC compared to WT was observed. In-silico modeling of WT, N74D, and N74T rotamers showed steric compatibility for N74T, whereas N74D introduced pocket clashes and electrostatic repulsion with LEN's sulfonamide (Figure S1, Supplemental Digital Content, <http://links.lww.com/QAD/D835>) [14]. These results indicate that N74T is not associated with LEN resistance.

Discussion

The findings from Phase 2 of the ARTISTRY-1 study demonstrated that a once-daily regimen of BIC+LEN maintained high rates of virologic suppression in PWH who transitioned from complex ART regimens, despite a high prevalence of baseline RT and PR RAMs. Although not unexpected due to the lack of cross-resistance between BIC or LEN and these RT and PR mutants, these results indicate that the BIC+LEN treatment combination was as efficacious as the complex regimens that participants were receiving prior to switching to BIC+LEN.

One of the preferred regimens for the treatment of HIV is the guideline recommended daily STR of BIC, emtricitabine (FTC), and tenofovir alafenamide (TAF) (B/F/TAF, BIKTARVY) [1]. Although B/F/TAF is indicated in PWH harboring the M184I/V RT RAM without additional RAMs, the presence of M184I/V alone was detected in only 10% of participants in this study (Table 1) and greater than half of participants with M184I/V had ≥ 3 TAMs. In this context, the use of B/F/TAF would not be indicated as the presence of ≥ 3 TAMs confer resistance to both TAF and FTC. As a result, the availability of the STR containing BIC and LEN would offer a viable option for convenient daily dosing in this population.

Although there was a chance imbalance of participants with INSTI RAMs at randomization (9/10 participants with INSTI RAMs were in the BIC+LEN 25 mg arm), all participants with baseline INSTI RAMs were virologically suppressed at Week 48. The overall number was small (10/128; 7.8%), limiting the power to assess mutation-level effects on long-term BIC+LEN efficacy. Because baseline INSTI resistance was ascertained from proviral DNA genotyping, the detected INSTI RAMs in the archived reservoir may not have reflected actively circulating replication-competent virus, which could have confounded the interpretation of their impact on treatment response. Additionally, all detected mutations were mixtures with WT, and most participants harbored RAMs associated with first-generation INSTIs that are known to have no effect on BIC susceptibility. These findings suggest that BIC+LEN maintained its effectiveness even in the context of archived INSTI resistance.

Only one participant with extensive prior ART exposure and baseline resistance to multiple drug classes (NRTIs, NNRTIs, and PIs) met the criteria for resistance testing. No emergent INSTI mutations were detected, however, a novel capsid substitution (N74T) was identified at a known position associated with LEN resistance (N74D). Importantly, extensive phenotypic characterization of N74T using SDM and multiple assays demonstrated no changes in LEN susceptibility, with EC_{50} s similar to wild-type levels. In contrast, the N74D mutant used as a control showed substantial reductions in LEN susceptibility, validating the assays' sensitivity. These findings

confirm that N74T is a CA polymorphism with no impact on LEN susceptibility. Of note, the participant resuppressed after switching to a LEN-containing regimen. Furthermore, the codons for threonine at position 74 are ACG/A/C/T, while those for aspartic acid are GAT/C. A mutation from N74T to the known LEN RAM N74D would require two nucleotide changes, making such a transition unlikely and further supporting the limited clinical relevance of N74T.

Although participants had almost exclusively HIV-1 subtype B, prior data on BIC and LEN [15–17] suggest that response to BIC+LEN is expected to be similar across all HIV-1 subtypes. Ongoing Phase 3 studies will provide additional information on overall response to BIC+LEN.

Together, these results support the benefit of BIC+LEN as an optimized, effective regimen for virologically suppressed individuals with complex treatment histories and resistance profiles. The absence of resistance emergence over 48 weeks reinforces the potential durability of the BIC+LEN combination regimen and its potential role in managing long-term HIV care in PWH who are suppressed but taking complex treatment regimens.

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Author contributions: N.P., C.C. and N.A.M. conceptualized the study and wrote the manuscript. N.P. and V. N. performed the drug susceptibility experiments. N.P. performed the structural in silico modeling. J.M.M. and P. S. provided critical review of the final text. All authors contributed to the review and editing of the manuscript.

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Conflicts of interest

N.P., V.N., M.M., P.S., C.C., and N.M. are employees and stockholders of Gilead Sciences, Inc., which funded the study.

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