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Lenacapavir (LEN) Investigational Use With Bictegravir

This document is in response to your request for information regarding the investigational use of bictegravir (BIC) with lenacapavir (LEN) for the treatment of HIV-1.

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Summary

Clinical Data on Use of LEN With BIC

ARTISTRY-1: An ongoing phase 2/3 study is evaluating the efficacy and safety of switching to BIC + LEN vs continuing a complex ART regimen in VS PWH.[1]

Results from phase 2 through Week 96 have been reported.[1-3]

- Through Week 48, high rates of virologic suppression were maintained in each group: BIC 75 mg + LEN 25 mg, 92.2%; BIC 75 mg + LEN 50 mg, 90.4%; and complex ART regimen, 100%.[1] Virologic suppression rates were similar between the complex ART regimen group and both BIC + LEN groups and between participants with and without RAMs at baseline.[4]
- Through Week 48, all commonly reported TEAEs (≥5% in any group) were Grade 1 or 2 in severity, except for 1 case of Grade 3 diarrhea unrelated to study drug. TEAEs led to treatment DC in 2% of participants in the BIC 75 mg + LEN 25 mg group, 1.9% in the BIC 75 mg + LEN 50 mg group, and 0% in the complex ART regimen group.[1]
- Among participants initially randomized to the BIC 75 mg + LEN 50 mg group, virologic suppression was maintained through Week 96 (96%; 45/47). Within this group, 25% reported Grade ≥3 AEs, and 17.3% reported SAEs.[3]

Results from phase 3 through Week 48 have been reported.[5]

- High rates of virologic suppression were maintained in each group: BIC/LEN STR 75 mg/50 mg, 96%, and complex ART regimen, 94%. BIC/LEN was non-inferior to complex ART regimens in the maintenance of virologic suppression.
- In the BIC/LEN and complex ART regimen groups, the rates of Grade ≥3 AEs (each, 14%) and DCs due to AEs (2% vs 1%) were similar.

ARTISTRY-2: An ongoing phase 3 study is evaluating the efficacy and safety of switching from BIC/FTC/TAF to BIC/LEN STR 75 mg/50 mg vs continuing BIC/FTC/TAF in VS PWH.[6]

- Through Week 48, virologic suppression rates were high in both groups: BIC/LEN 75 mg/50 mg, 93.5%; BIC/FTC/TAF, 90.6%. BIC/LEN was non-inferior to BIC/FTC/TAF in maintaining virologic suppression.

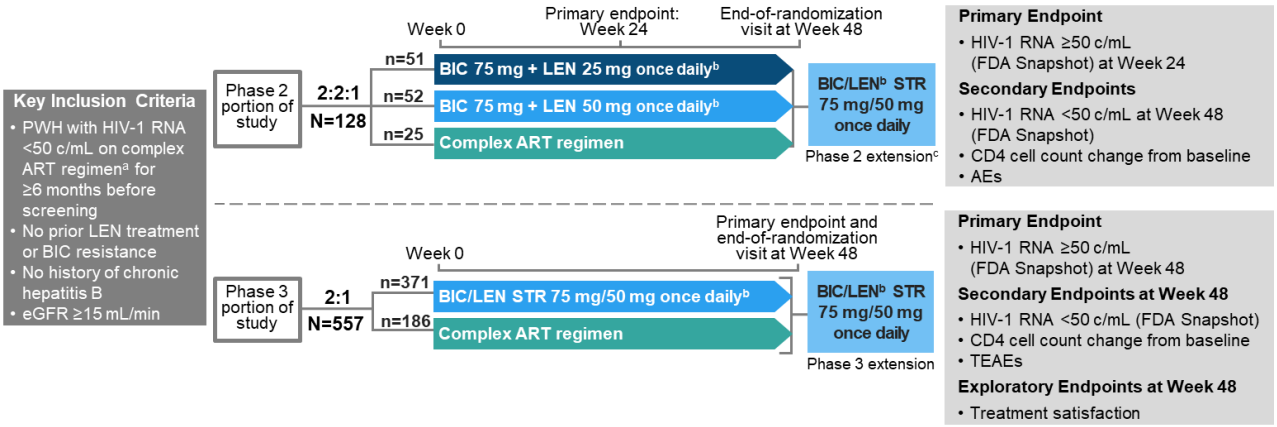
- Through Week 48, in the BIC/LEN and BIC/FTC/TAF groups, the rates of Grade ≥3 AEs (9.9% vs 7.9%, respectively) and DCs due to AEs (each, 1.6%) were similar.

Clinical Data on Use of BIC With LEN

ARTISTRY-1: Switching to BIC + LEN vs Complex ART

An ongoing, randomized, multicenter, open-label, phase 2/3 study (NCT05502341) is evaluating the efficacy and safety of switching to BIC + oral LEN vs continuing their ART regimen in PWH who were receiving a complex ART regimen.[1,2]

Figure 1. ARTISTRY-1 Phase 2/3: Study Design[1-3,5,7-9]



[a]Due to viral resistance, intolerance, or contraindication to existing STRs. Regimens contained the following: a boosted PI or NNRTI + ≥1 other third agent from a class other than NRTIs, or ≥2 pills/day or a dosing frequency >once daily, or parenteral ART (excluding a complete long-acting injectable regimen) plus oral ART.
[b]Oral loading doses of LEN (600 mg for 2 days) were given after participants switched from their complex ART regimen.
[c]All participants reached the Week 48 timepoint and completed the end-of-randomization visit before entering the OLE phase.

Phase 2 of ARTISTRY-1

During the phase 2 portion of the study, participants were randomly assigned to switch to BIC 75 mg + LEN (25 or 50 mg; oral) or to continue their complex ART regimen. After the randomized period, participants could continue on to the extension period and receive BIC/LEN STR (Figure 1).[1]

Table 1. Phase 2 of ARTISTRY-1: Baseline Demographics, Disease Characteristics, and Historical Resistance Mutations[2]

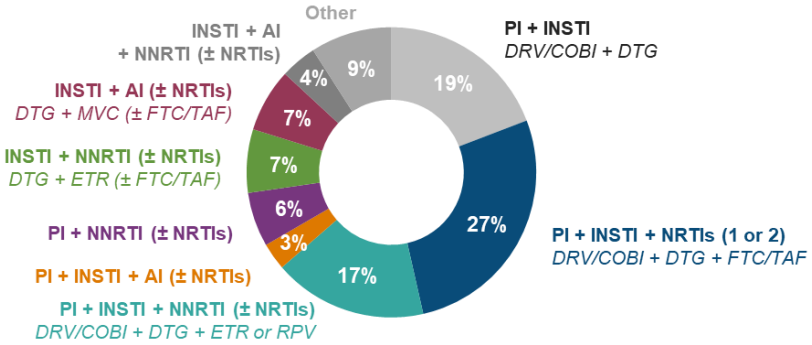
Key Demographics and Characteristics	BIC 75 mg + LEN 25 mg (n=51)	BIC 75 mg + LEN 50 mg (n=52)	Complex ART Regimen (n=25)	Total (N=128)
Age, median (range), years	62 (26–79)	62 (34–76)	58 (41–70)	60 (26–79)
Female sex assigned at birth, n (%)	13 (25.5)	7 (13.5)	4 (16)	24 (19)
Race, White/Black/Asian/other, %	56.9/35.3/3.9/3.9	65.4/30.8/3.8/0	80/20/0/0	64.8/30.5/3.1/1.6
Hispanic/Latinx,[a] n (%)	7 (14)	9 (17.6)	4 (16)	20 (15.9)
CD4 count, median (IQR), cells/mcL	583 (460–764)	624 (517–791)	585 (285–733)	610 (435–766)
<200 cells/mcL, n (%)	1 (2)	1 (1.9)	2 (8)	4 (3.1)

Key Demographics and Characteristics		BIC 75 mg + LEN 25 mg (n=51)	BIC 75 mg + LEN 50 mg (n=52)	Complex ART Regimen (n=25)	Total (N=128)
Duration of HIV treatment,[b] median (IQR), years		27.8 (22.7–32.4)[c]	27 (18.9–31.5)	26.9 (19.8–31.9)	27 (19.9–32)
Prior ARTs,[d] median (IQR), n		4 (2–9)	7 (3–11)	8 (3–13)	6 (3–11)
Reasons for complex regimen,[e] n (%)	History of resistance	44 (86.3)	40 (76.9)	20 (80)	104 (81.3)
	Intolerance of STR components	20 (39.2)	11 (21.2)	7 (28)	38 (29.7)
	Contraindications to STRs	7 (13.7)	4 (7.7)	1 (4)	12 (9.4)
ARTs,[d] median (range), n		2 (2–5)	2.5 (2–5)	3 (2–5)	2 (1–5)
Pills/day, median (range)		2 (2–8)	3 (2–9)	3 (2–8)	3 (2–9)
Historical resistance mutations,[e] n (%) INSTI/NNRTI/NRTI/PI		0/49/60.8/ 35.3	0/53.8/67.3/ 32.7	0/56/64/44	0/52.3/64.1/ 35.9

[a]Ethnicity data were not permitted to be collected for 1 patient each in the BIC 75 mg +LEN 25 mg and BIC 75 mg + LEN 50 mg arms.
[b]Calculated with the following equation: (date of first dose – start date of first HIV treatment + 1 day)/365.25.
[c]n=50.
[d]Defined as ARTs taken on Day 1 or up to 14 days before Day 1. If participants received multiple ARTs, they were counted once per participant for each drug name and ART class.
[e]Categories were not mutually exclusive. An alternative response was "no" or "not available."

Refer to Figure 2 for a summary of complex ART regimens at baseline; 53 participants (41.4%) in the overall population were taking twice-daily ART, and 43%, 18.8%, 10.9%, and 27.3% were taking 2, 3, 4, or ≥5 pills/day, respectively.[2]

Figure 2. Phase 2 of ARTISTRY-1: Complex ART Regimens at Baseline (N=128)[2]



Abbreviation: AI=attachment inhibitor.
Note: Regimens in italics were the most common regimen in each category; not all regimens are shown here. Percentages do not equal 100% due to rounding.

A separate analysis assessed the presence of RAMs at baseline with historical genotypic reports, and retrospective proviral DNA analysis, which identified the following (Table 2)[4]:

- High level of resistance to NRTI, NNRTI, and PI classes at baseline
- High prevalence of M184V/I and TAMs at baseline

Table 2. Phase 2 of ARTISTRY-1: Baseline Preexisting Resistance Mutations, and NRTI Mutations by Treatment Group[4]

Baseline Resistance Mutations, %	BIC 75 mg + LEN 25 mg (n=51)	BIC 75 mg + LEN 50 mg (n=52)	Complex ART Regimen (n=25)	Total (N=128)
Preexisting resistance mutations by ARV class,[a] NRTI/NNRTI/PI/INSTI	86/60/44/26	75/65/40/0	83/74/61/5	81/65/46/11

Baseline Resistance Mutations, %		BIC 75 mg + LEN 25 mg (n=51)	BIC 75 mg + LEN 50 mg (n=52)	Complex ART Regimen (n=25)	Total (N=128)
Preexisting NRTI mutations[b]	M184V/I	72	67	70	70
	K65R	10	8	13	10
	≥3/≥4 TAMs	52/32	42/33	26/9	43/28

[a]NRTI, NNRTI, and PI data were available in 124 participants; INSTI data were available in 94 participants. Baseline RAM data were evaluated using historical genotypes and retrospective proviral DNA analysis.
[b]TAMs included M41L, D67N, K70R, L210W, T215Y/F, and K219E/N/Q/R in RT; 11% had M184V/I alone.

Efficacy, immunological, and resistance outcomes through Week 48

At Week 24, 1 participant (1.9%) in the BIC 75 mg + LEN 50 mg group and no participants in the BIC 75 mg + LEN 25 mg group or complex ART regimen group had HIV-1 RNA ≥50 c/mL (primary endpoint; FDA Snapshot algorithm).[2] At Week 48, similarly high rates of virologic suppression were maintained in each group (Table 3).[1]

Table 3. Phase 2 of ARTISTRY-1: Rates of HIV RNA <50 c/mL (FDA Snapshot) and HIV RNA ≥50 c/mL at Week 48[1]

Efficacy Endpoints	BIC 75 mg + LEN 25 mg	BIC 75 mg + LEN 50 mg	Complex ART Regimen
HIV-1 RNA ≥50 c/mL, % (n/N)	3.9 (2/51)	1.9 (1/52)	0 (0/25)
Difference, % (95% CI); *P*-value	3.9 (−10.7, 13.9); 1	1.9 (−12.2, 10.7); 1	–
HIV-1 RNA <50 c/mL, % (n/N)	92.2 (47/51[a])	90.4 (47/52[b])	100 (25/25)
Difference, % (95% CI); *P*−value	−7.8 (−19.2, 7); 0.3	−9.6 (−21, 5.3); 0.17	–

[a]Reasons for DC before Week 48: AE and participant decision (each, n=1).
[b]Reasons for DC before Week 48: AE, death, participant decision, and investigator decision (each, n=1).
Note: *P*-values were for comparisons vs the complex ART regimen and are reported for descriptive purposes.

Three participants had HIV RNA levels ≥50 c/mL: 2 participants (3.9%) in the BIC 75 mg + LEN 25 mg group were resuppressed at their next study visit without a change in ART (HIV-1 RNA at Week 48: 50 c/mL and 98 c/mL, respectively), and 1 participant (1.9%) in the BIC 75 mg + LEN 50 mg group (HIV-1 RNA at Week 48: 305 c/mL) was resuppressed by Day 368 after switching treatment to DTG + MVC + LEN SUBQ. The third participant underwent a resistance analysis, and the N74T capsid mutation was noted with PhenoSense assay failure; this novel capsid polymorphism did not confer resistance to LEN and no change in BIC sensitivity occurred.[1,4]

At Week 48, the median (Q1, Q3) change in CD4 cell counts from baseline to Week 48 were as follows: BIC 75 mg + LEN 25 mg, +29 (−45, +96) cells/mcL; BIC 75 mg + LEN 50 mg, +48 (−59, +150) cells/mcL; complex ART regimen, +31 (−46, +111) cells/mcL.[1]

Through Week 48, participants with and without NRTI, NNRTI, PI, and INSTI RAMs had high rates of virologic suppression, and were similar between participants with and those without RAMs within each treatment group (Table 4).[4]

Table 4. Rates of HIV RNA <50 c/mL at Week 48 Overall and by Baseline Resistance Category (FDA Snapshot)[1,4]

HIV-1 RNA <50 c/mL, % (n/N)		BIC 75 mg + LEN 25 mg	BIC 75 mg + LEN 50 mg	Complex ART Regimen	Overall
Overall		92.2 (47/51[a])	90.4 (47/52[b])	100 (25/25)	93 (119/128)
Difference, % (95% CI); *P*-value vs complex ART regimen		−7.8 (−19.2, 7); 0.3	−9.6 (−21, 5.3); 0.17	–	–
NRTI RAMs[c]	Yes	92.5 (37/40)	91.9 (34/37)	100 (18/18)	93.7 (89/95)
	No	88.9 (8/9)	86.7 (13/15)	100 (5/5)	89.7 (26/29)

HIV-1 RNA <50 c/mL, % (n/N)		BIC 75 mg + LEN 25 mg	BIC 75 mg + LEN 50 mg	Complex ART Regimen	Overall
NNRTI RAMs[c]	Yes	92.6 (25/27)	93.5 (29/31)	100 (16/16)	94.6 (70/74)
	No	90.9 (20/22)	85.7 (18/21)	100 (7/7)	90 (45/50)
PI RAMs[c]	Yes	100 (22/22)	88.2 (15/17)	100 (12/12)	96.1 (49/51)
	No	85.2 (23/27)	91.4 (32/35)	100 (11/11)	90.4 (66/73)
INSTI RAMs[c]	Yes	88.9 (8/9)[d]	0	100 (1/1)	90 (9/10)
	No	88.5 (23/26)	89.7 (35/39)	100 (19/19)	91.7 (77/84)

[a]Reasons for DC before Week 48: AE and participant decision (each, n=1).
[b]Reasons for DC before Week 48: AE, death, participant decision, and investigator decision (each, n=1).
[c]Nominal *P*>0.05 values for all comparisons between those with and without each RAM within each treatment group.
[d]One participant discontinued treatment but was VS at their last study visit.
Note: P-values were for comparisons vs the complex ART regimen and are reported for descriptive purposes only.

Safety results through Week 48

Through Week 48, the safety profile of BIC + LEN was similar regardless of LEN dose. Common TEAEs (≥5% in any group) were Grade 1 or 2 in severity, except for 1 case of Grade 3 diarrhea, which was deemed unrelated to study drug (Table 5).[1]

Table 5. Phase 2 of ARTISTRY-1: TEAEs Through Week 48[7]

Safety Outcomes, n (%)		BIC 75 mg + LEN 25 mg (n=51)	BIC 75 mg + LEN 50 mg (n=52)	Complex ART Regimen (n=25)
Any TEAE		42 (82.4)	41 (78.8)	19 (76)
Grade ≥3 TEAEs		7 (13.7)	4 (7.7)	1 (4)
Treatment-related TEAEs		9 (17.6)	3 (5.8)	0
Serious TEAEs		4 (7.8)[a]	3 (5.8)[a]	3 (12)[a]
TEAEs that led to treatment DC		1 (2)[b]	1 (1.9)[c]	0
TEAEs (≥5% in either LEN group)	COVID-19	8 (15.7)	5 (9.6)	4 (16)
	Diarrhea	5 (9.8)	2 (3.8)	1 (4)
	Nasopharyngitis	5 (9.8)	0	1 (4)
	Cough	4 (7.8)	3 (5.8)	0
	URTI	3 (5.9)	4 (7.7)	2 (8)
	Arthralgia	3 (5.9)	4 (7.7)	0
	Constipation	3 (5.9)	2 (3.8)	0
	Nausea	3 (5.9)	2 (3.8)	0
	Vertigo	3 (5.9)	0	0
	HTN	1 (2)	5 (9.6)	1 (4)
	Pain in extremity	1 (2)	3 (5.8)	1 (4)
Death		0	1 (1.9)[d]	0

[a]Deemed unrelated to study treatment. [b]Grade 1 nausea was reported on Day 1.
[c]Grade 3 worsening of vomiting was reported in a participant with prior history of nausea and vomiting.
[d]Death was due to coronary artery disease and was deemed unrelated to study drug.

At Week 24, Grade 3 and 4 treatment-emergent laboratory abnormalities were experienced by 9.8% and 2% of participants, respectively, in the BIC 75 mg + LEN 25 mg group; by 17.3% and 5.8% in the BIC 75 mg + LEN 50 mg group; and by 32% and 0% in the complex ART regimen group.[10] Laboratory abnormalities were not reported at Week 48.[1,11]

In general, with BIC + LEN treatment, most fasting lipid parameters decreased at Week 48, whereas increases in fasting glucose levels, body weight, and BMI were observed (Table 6). Rates of treatment-emergent metabolic disorders are summarized in Table 6.[12]

Table 6. Phase 2 of ARTISTRY-1: Median Changes in Metabolic Parameters at Week 48 and Treatment-Emergent Metabolic Disorders[1,12]

		BIC 75 mg + LEN 25 mg (n=51)	BIC 75 mg + LEN 50 mg (n=52)	Complex ART Regimen (n=25)
Metabolic parameter, median change from baseline[a]	Total cholesterol, mg/dL	−21	−14	+4
	LDL cholesterol, mg/dL	−10	−11	+5
	HDL cholesterol, mg/dL	−2	0	-3
	Triglycerides, mg/dL	−18	−9	+6
	Total:HDL cholesterol ratio	−0.3	−0.4	+0.2
	Fasting glucose, mg/dL	+3	+2	-6
	Body weight,[b] kg	+0.6 (−0.6, +1.9)	+0.9 (−2.1, +3.3)	-0.7 (-2.4, +0.2)
	BMI, kg/m^2	+0.2	+0.3	-0.2
	Systolic/diastolic BP, mm Hg	−5/−1	+2/+2	0/+1
Treatment-emergent metabolic disorders,[c] CKD/DM/HTN/dyslipidemia, n (%)		3 (6)/2 (4)/ 1 (2)/ 0	1 (2)/2 (4)/ 6 (12)[d]/0	1 (4)/1 (4)/ 1 (4)/ 0

[a]Results shown from participants with available data at both baseline and Week 48.
[b]Q1, Q3 were reported for the change from baseline to Week 48.
[c]Referred to grouped Standardized Medical Dictionary for Regulatory Activities Query. Disorders began at the beginning of the study and up to 60 days after stopping BIC or LEN (BIC + LEN groups) or at the beginning of the study and up to 30 days after stopping the complex ART regimen. Multiple AEs were counted once per participant.
[d]Included HTN (n=5) and hypertensive crisis (n=1). All cases were reported among participants who had abnormal BP (systolic/diastolic BP, >120/>80 mm Hg), and none were deemed to be drug related.

Efficacy and safety through Week 96: participants initially randomized to the BIC 75 mg + LEN 50 mg group[3]

Efficacy and safety outcomes through Week 96 were analyzed for participants who were initially randomized to the BIC 75 mg + LEN 50 mg group (n=52). Of these participants, 5 discontinued from the study during the randomized phase and 47 continued in the OLE.

Virologic suppression was maintained in 96% of participants (45/47; missing=excluded) through Week 96. The 2 participants with HIV-1 RNA ≥50 c/mL had low-level viremia (defined as HIV-1 RNA <500 c/mL) and were later resuppressed without requiring a change in their ART regimen. One of these participants met criteria for resistance testing and had assay failures for all genes. The median (Q1, Q3) change from baseline to Week 96 in CD4 count was -6 (-118, 123) cells/mcL.

Through Week 96, 46 participants (88.5%) reported an AE, including 13 (25%) with a Grade ≥3 AE. Nine participants (17.3%) reported SAEs, 3 (5.8%) TRAEs were reported (atrial conduction time prolongation, decreased BP, and nausea and vomiting), and no serious TRAEs were reported. No new AEs led to treatment DCs and no deaths were reported between Week 48 and Week 96. The most common (≥10%) AEs reported through Week 96 were URTI (19.2%), COVID-19 (17.3%), HTN (13.5%), arthralgia (11.5%), and cough (11.5%). The median (Q1, Q3) change from baseline to Week 96 in weight was 0 (-3, 2.7) kg.

Phase 3 of ARTISTRY-1

For the phase 3 portion of the study, participants were randomly assigned (2:1) to receive an STR of BIC/LEN 75 mg/50 mg (n=371) or continue their stable complex ART regimen (n=186) for 48 weeks (Figure 1). At baseline, participants had a history of resistance to multiple drug classes (Table 7).[3]

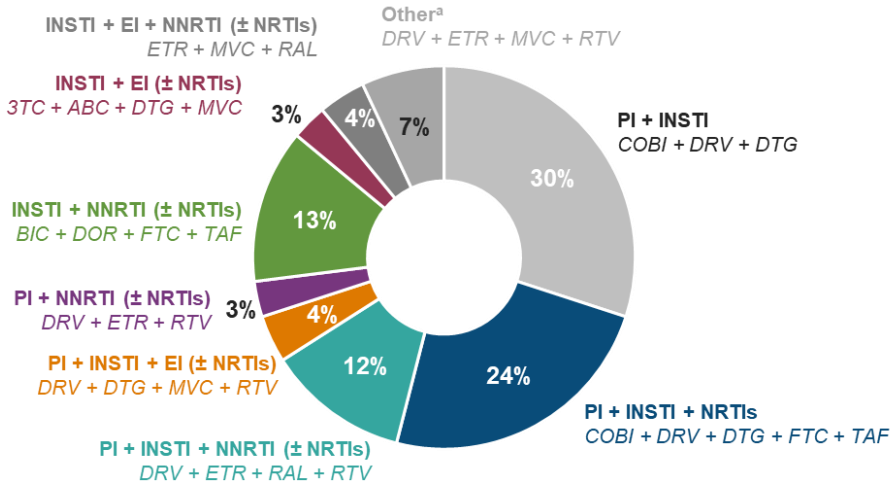
Table 7. Phase 3 of ARTISTRY-1: Baseline Demographics, Disease Characteristics, and Preexisting Resistance Mutations[3]

Key Demographics and Characteristics		BIC/LEN 75 mg/50 mg (n=371)	Complex ART Regimen (n=186)	Overall (N=557)
Age, median (range), years		60 (22–84)	60 (24–75)	60 (22–84)
Female sex assigned at birth, n (%)		64 (17)	36 (19)	100 (18)
Race, White/Black/Asian/other,[a] %		70/17/4/3	67/18/5/2	69/17/4/3
Hispanic/Latinx,[b] n (%)		80 (22)	42 (23)	122 (22)
CD4 count, median (IQR), cells/mcL		626 (457–836)[c]	579 (450–747)[d]	612 (456–809)[e]
Duration of HIV treatment, median (IQR), years		28.3 (21.6–32.3)[f]	28.3 (21.4–31.8)[g]	28.3 (21.6–32.1)[h]
ARV pills/day, median (range), n		3 (2–11)	3 (2–9)	3 (2–11)
Reasons for taking complex regimen,[i] n (%)	History of resistance	297 (80)	153 (82)	450 (81)
	Intolerance to STR components	89 (24)	39 (21)	128 (23)
	Contraindications to STR components	23 (6)	10 (5)	33 (6)
History of selected comorbidities,[i,j] dyslipidemia/HTN/DM or hyperglycemia/CKD, %		66/51/25/13	72/48/23/16	68/50/24/14
Historical drug class resistance,[i,k] n (%)	NRTI	247 (67)	128 (69)	375 (67)
	NNRTI	203 (55)	104 (56)	307 (55)
	PI	151 (41)	77 (41)	228 (41)
	INSTI	1 (<1)	2 (1)	3 (1)

[a]Local regulations did not permit the collection of race data for 19 participants in the BIC/LEN group and 17 in the complex ART regimen group. The "other" category included participants who were American Indian or Alaska Native, Native Hawaiian, Pacific Islander, or other.
[b]Local regulations did not permit the collection of ethnicity data for 21 participants in the BIC/LEN group and 16 in the complex ART regimen group.
[c]n=366. [d]n=185. [e]n=551.
[f]n=358. [g]n=183. [h]n=541.
[i]Not mutually exclusive.
[j]Grouped terms per MedDRA.
[k]NRTI, NNRTI, PI, and INSTI data were not available for 75, 79, 78, and 197 participants in the BIC/LEN group, respectively, and 44, 46, 50, and 100 participants in the complex ART regimen group. The denominator used for percentage calculations was the total number of participants.

Refer to Figure 3 for a summary of complex ART regimens; 77% of participants (n=427) were receiving a PI at baseline, and 75% of those participants (n=419) received a boosted PI-based regimen. At baseline, 39% of overall participants were receiving twice-daily ART, and 41%, 26%, 11%, and 22% were taking 2, 3, 4, or ≥5 pills/day, respectively.[3,13]

Figure 3. Phase 3 of ARTISTRY-1: Complex ART Regimens at Baseline[3]



Abbreviations: 3TC=lamivudine; ABC=abacavir; EI=entry inhibitor.
[a]Other regimens could have contained a PI.
Note: Regimens in italics were the most common regimen in each category.

Efficacy outcomes through Week 48

The median (Q1, Q3) exposure in the BIC/LEN group was 65.9 (56.6, 74) weeks and 65.9 (55.6, 73.9) weeks in the complex ART group. BIC/LEN was non-inferior to complex ART regimens in maintaining virologic suppression at Week 48 (Table 8).[3] Each of the participants in the BIC/LEN group with HIV-1 RNA ≥50 c/mL at Week 48 achieved virologic resuppression or had low-level viremia without changes in their ART regimen.[13]

Table 8. Phase 3 of ARTISTRY-1: Rates of HIV RNA ≥50 c/mL and HIV RNA <50 c/mL (FDA Snapshot) at Week 48 in the Full Analysis Set[3]

Efficacy Endpoints	BIC/LEN 75 mg/50 mg	Complex ART Regimen
HIV-1 RNA ≥50 c/mL, % (n/N)	1 (3/371)	1 (2/186)
Difference,[a] % (95.002% CI)	−0.3 (−2.3, 1.8)	
HIV-1 RNA <50 c/mL, % (n/N)	96 (356/371)	94 (174/186)
Difference, % (95.002% CI)	2.4 (-1.8 to 6.6)	
No virologic data, % (n/N)	3 (12/371)[b]	5 (10/186)[c]

[a]Two-sided CI was based on Mantel-Haenszel stratum weights and Koch variance estimator and was adjusted by geographic region (US vs non-US).
[b]Reasons for DC before Week 48: AE or death, n=7 (AEs, n=5; deaths, n=2); other reasons and last HIV-1 RNA <50 c/mL, n=5.
[c]Reasons for DC before Week 48: other reasons and last HIV-1 RNA <50 c/mL, n=8; AE or death, n=1; and missing data but still on study drug, n=1.

CD4 counts remained stable in both groups, with a median (IQR) change in CD4 count from baseline to Week 48 of +18 (-72 to 98) cells/mcL in the BIC/LEN group and -12 (-82 to 93) cells/mcL in the complex ART group (difference in change: +19; 95% CI: -11.6 to 49.5; *P*=0.22).[3]

Through Week 48, 3 participants qualified for resistance testing and no treatment-emergent resistance was detected.[3]

Safety and treatment satisfaction outcomes through Week 48

Between groups, similar rates of AEs and SAEs were reported, most AEs were mild to moderate in severity, and the incidence of treatment DC due to AEs was low (Table 9).

The incidence of renal-related AEs was low and the safety profile was similar between treatment groups regardless of the level of renal function.[3]

Table 9. Phase 3 of ARTISTRY-1: Safety Outcomes Through Week 48[3,9]

Safety Outcomes, n (%)		BIC/LEN 75 mg/50 mg (n=371)	Complex ART Regimen (n=186)
AE		305 (82)	157 (84)
TRAE		53 (14)	3 (2)
Grade ≥3 AE		51 (14)	26 (14)
Grade ≥3 TRAE		2 (1)[a]	0
SAE		52 (14)	22 (12)
Treatment-related SAE		1 (<1)[b]	0
AE that led to study drug DC		6 (2)[c]	1 (1)[d]
AEs with ≥5% frequency in the BIC/LEN group	URTI	34 (9)	24 (13)
	Headache	28 (8)	4 (2)
	Nasopharyngitis	26 (7)	17 (9)
	Diarrhea	22 (6)	11 (6)
	HTN	21 (6)	6 (3)
	COVID-19	20 (5)	6 (3)
	Arthralgia	19 (5)	8 (4)
	Cough	18 (5)	11 (6)
Death		5 (1)[e]	0
Any-grade laboratory abnormality		341 (92)	178 (97)[f]
Grade ≥3 laboratory abnormality		124 (33)	64 (35)[f]

[a]DM and maculopapular rash. [b]DM was newly diagnosed in a participant who had a high fasting glucose level at baseline. This resolved on Day 173 after a switch in ARV regimen to EFV + DRV/RTV on Day 103.
[c]Cerebrovascular accident; DM; erectile dysfunction and worsened HTN; headache and hypoesthesia; HBV viremia; and alopecia, dizziness, worsened fatigue, headache, and nausea (each, n=1). All AEs except for hypoesthesia, HBV viremia, and cerebrovascular accident were related to BIC/LEN.
[d]Pulmonary embolism; unrelated to study drug.
[e]None of the deaths were deemed related to BIC/LEN: unknown cause (n=2), metastatic neoplasm (n=1), cardiac arrest (n=1), and respiratory failure (n=1). [f]n=183.

From baseline to Week 48, body weight remained stable in both groups, with a median (IQR) change of +0.6 (-1.1 to 2.6) kg in the BIC/LEN group and 0 (-2 to 2.4) kg in the complex ART regimen group.[3]

After switching to BIC/LEN, fasting levels of TC, LDL, and TG, and the TC:HDL ratio was observed to improve from baseline to Week 48; HDL levels remained stable (Table 10).[3]

Table 10. Phase 3 of ARTISTRY-1: Changes in Fasting Lipids From Baseline to Week 48[3,9]

	TC		LDL		HDL		TG		TC:HDL	
	BL[a]	Change From BL to Week 48[b]	BL[a]	Change From BL to Week 48[b]	BL[a]	Change From BL to Week 48[b]	BL[a]	Change From BL to Week 48[b]	BL[a]	Change From BL to Week 48[b]
BIC/LEN[c]	176	-15	97	-9	47	-1	130	-15	3.6	-0.3
Complex ART Regimen[d]	188	+2	105	+2	48	0	123	+4	3.7	0
P-Value[e]	<0.0001		<0.0001		0.46		0.0008		<0.0001	

Abbreviation: BL=baseline.
[a]Median value; presented as mg/dL. [b]Median change from baseline; presented as mg/dL.
[c]Baseline, n=316. [d]Baseline, n=147.
[e]Nominal *P*-values for comparison between treatment groups were estimated using the mixed model with repeated measures of the change from BL (fixed effects: treatment, visit, treatment by visit, BL value, and geographic region [US vs non-US]; random effect: participant).

HIVTSQs scores were similar between groups at baseline in the BIC/LEN (n=359; mean ± SD score, 55±10.4) and complex ART regimen groups (n=178; mean ± SD score, 55±9.4). After switching from a complex ART regimen to BIC/LEN, HIVTSQs scores improved from baseline through Week 48 (n=344; mean change, +7), whereas the score in the complex ART regimen group did not change through Week 48 (n=165). The difference in treatment satisfaction scores between groups was nominally greater at Week 48 (*P*<0.0001). Post-switch to BIC/LEN, the mean ± SD increase from baseline to Week 48 in HIVTSQc score was 27±9.1.[3,9]

DDI analysis: comparison of potential DDI liability with BIC/LEN vs other frequently prescribed complex regimens[14]

The DDI profiles of BIC/LEN and the 6 most commonly used complex ART regimens in the phase 3 portion of ARTISTRY-1 study were compared. The DDI profiles of each regimen with the 10 most frequently prescribed medications in the US and the 8 medications most commonly prescribed in elderly participants were assessed. The Liverpool HIV Drug Interactions database and/or the US prescribing information were utilized to inform the DDI profiles.

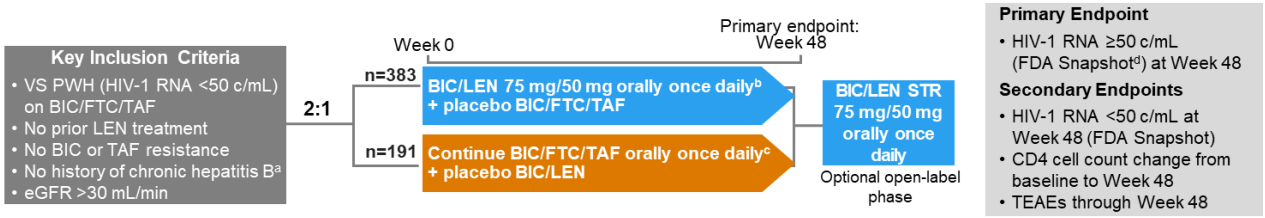
More potential DDIs were observed for boosted PI-based regimens than for BIC/LEN, which was likely due to the stronger inhibition of CYP3A and P-gp metabolic pathways by PK boosters, such as COBI and RTV, than with LEN (a moderate CYP3A inhibitor and weak inhibitor of P-gp).

Medications listed as having potential DDIs with BIC/LEN were as follows: clopidogrel (do not administer); amlodipine, apixaban, fluticasone, metformin, simvastatin, and warfarin (potential interactions); and atorvastatin, prednisone, and rosuvastatin (potential weak interactions).

ARTISTRY-2: Switching to BIC/LEN vs Complex ART[6]

An ongoing, randomized, multicenter, double-blind, active-controlled phase 3 study (NCT06333808) is evaluating the efficacy and safety of switching from BIC/FTC/TAF to STR BIC/LEN 75 mg/50 mg vs continuing BIC/FTC/TAF in VS PWH. After the randomized period, participants could continue in the OLE phase and receive BIC/LEN.

Figure 4. ARTISTRY-2: Study Design[6]



Abbreviations: HBcAb=HBV core antibody; HBsAb=HBV surface antibody; HBsAg=HBV surface antigen.
[a]Determined by the following at the screening visit: either HBsAg+ and HBsAb-, regardless of HBcAb status, or HBcAb+ and HBsAb-, regardless of HBsAg status.
[b]Oral loading doses of LEN 600 mg on Days 1 and 2 were given.
[c]Participants were given placebo to match LEN on Days 1 and 2 of treatment.
[d]Non-inferiority margin: 4%.

Table 11. ARTISTRY-2: Baseline Demographics and Disease Characteristics[6]

Key Demographics and Characteristics	BIC/LEN 75 mg/50 mg (n=383)	BIC/FTC/TAF (n=191)	Total (N=574)
Age, median (range), years	47 (23–77)	51 (26–77)	49 (23–77)
Female sex assigned at birth, n (%)	69 (18)	42 (22)	111 (19.3)
Race, White/Black/Asian/other,[a] %	52/29.5/13.3/5.2	58.1/23/13.6/5.2	54/27.4/13.4/5.2
Hispanic/Latinx,[b] n (%)	106 (27.7)	49 (25.8)	155 (27.1)
CD4 count, median (Q1, Q3), cells/mcL	711 (547, 914)	663 (522, 873)	695 (541, 902)
History of select comorbidities,[c] dyslipidemia/HTN/DM or hyperglycemia/CKD, %	41.3/36.8/ 17.8/5.2	41.4/33/ 16.2/6.3	41.3/35.5/ 17.2/5.6
Number of select comorbidities, 1/≥2, n (%)	94 (24.5)/ 121 (31.6)	57 (29.8)/ 52 (27.2)	151 (26.3)/ 173 (30.1)

[a]"Other" included participants who were Alaska Native, Native Hawaiian, Pacific Islander, and other.
[b]Local regulations did not permit the collection of ethnicity data for 1 participant in the BIC/FTC/TAF group and were excluded from the denominator.
[c]Grouped terms (per MedDRA); not mutually exclusive.

Efficacy outcomes through Week 48

The median (Q1, Q3) exposure to BIC/LEN was 60.6 (53, 69) weeks and 59.9 (52, 67.9) weeks for BIC/FTC/TAF. BIC/LEN was non-inferior to BIC/FTC/TAF in maintaining virologic suppression at Week 48 (Table 12).

Table 12. ARTISTRY-2: Rates of HIV RNA ≥50 c/mL and HIV RNA <50 c/mL (FDA Snapshot) at Week 48[6]

Efficacy Endpoints	BIC/LEN 75 mg/50 mg	BIC/FTC/TAF
HIV-1 RNA ≥50 c/mL, % (n/N)	1.3 (5/383)[a]	1 (2/191)
HIV-1 RNA <50 c/mL, % (n/N)	93.5 (358/383)	90.6 (173/191)
Difference,[b] % (95% CI)	0.3 (-1.9 to 2.4)	
No virologic data, % (n/N)	5.2 (20/383)[c]	8.4 (16/191)[d]

[a]Four of the 5 participants had low-level viremia (defined as HIV-1 RNA <1000 c/mL).
[b]Two-sided CI was based on Mantel-Haenszel stratum weights and the Koch variance estimator and was adjusted by geographic region (US vs non-US).
[c]Reasons for DC before Week 48: other reasons and last HIV-1 RNA was <50 c/mL, n=14; AE or death, n=6; other reasons and last HIV-1 RNA was ≥50 c/mL, n=3.
[d]Reasons for DC before Week 48: other reasons and last HIV-1 RNA was <50 c/mL, n=12; AE or death, n=4; other reasons and last HIV-1 RNA was ≥50 c/mL, n=2.

In the BIC/LEN group, 1 participant had an HIV-1 RNA of 10,700 c/mL at Week 48, was switched to a PI-containing regimen, and was resuppressed on the new regimen. Two participants in each group underwent resistance analysis. No treatment-emergent resistance was noted for 1 participant in the BIC/LEN group and for both participants in the BIC/FTC/TAF group. The other participant in the BIC/LEN group had a history of RAL and DTG exposure and had an isolated R263K integrase substitution recorded at Week 36; the R263K isolate was susceptible to BIC, and no capsid mutations were detected.

Through Week 48, CD4 cell counts remained stable.

Safety outcomes through Week 48

Similar rates of AEs and TRAEs were reported in both groups, and the overall incidence of treatment DC due to AEs was low (Table 13).

Table 13. ARTISTRY-2: Safety Outcomes Through Week 48[6]

Safety Outcomes, n (%)		BIC/LEN 75 mg/50 mg (n=383)	BIC/FTC/TAF (n=191)
AE		288 (75.2)	141 (73.8)
TRAE		40 (10.4)	23 (12)
Grade ≥3 AE		38 (9.9)	15 (7.9)
Grade ≥3 TRAE		1 (0.3)[a]	0
SAE		27 (7)	13 (6.8)
Treatment-related SAE		0	0
AE that led to study drug DC		6 (1.6)[b]	3 (1.6)[c]
AEs with ≥5% frequency in BIC/LEN group	Diarrhea	31 (8.1)	9 (4.7)
	Nasopharyngitis	30 (7.8)	13 (6.8)
	URTI	29 (7.6)	9 (4.7)
	Headache	22 (5.7)	6 (3.1)
	Nausea	20 (5.2)	11 (5.8)
Death		0	1 (0.5)[d]

[a]Grade 3 rhabdomyolysis.
[b]The following were deemed unrelated to BIC/LEN (each, n=1): anxiety; colon cancer; decreased libido; and encephalopathy and intracranial mass. The following were deemed related to BIC/LEN (each, n=1): alopecia and fatigue; and rash, restless leg syndrome, and trismus.
[c]The following were deemed unrelated to BIC/FTC/TAF (each, n=1): abdominal discomfort; road traffic accident. Dry mouth was deemed related to BIC/FTC/TAF treatment.
[d]Due to coronary artery disease and unrelated to study treatment.

At baseline, in the BIC/LEN and BIC/FTC/TAF groups, the median weight was the same (81.1 kg), and the median change from baseline to Week 48 was stable (-0.2 kg vs 0 kg, respectively).

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Abbreviations

AE=adverse event
ART=antiretroviral therapy
ARV=antiretroviral
BIC=bictegravir
BP=blood pressure
c/mL=copies per mL
CD4=cluster of differentiation
CKD=chronic kidney disease
COBI=cobicistat
DC=discontinuation
DDI=drug-drug interaction
DM=diabetes mellitus
DOR=doravirine
DRV=darunavir
DTG=dolutegravir
ETR=etravirine
FTC=emtricitabine
HIVTSQc=HIV Treatment Satisfaction Questionnaire change version
HIVTSQs=HIV Treatment Satisfaction Questionnaire status version
HTN=hypertension
INSTI=integrase strand transfer inhibitor
LEN=lenacapavir
MedDRA=Medical Dictionary for Regulatory Activities
MVC=maraviroc
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OLE=open-label extension
P-gp=P-glycoprotein
PI=protease inhibitor
PK=pharmacokinetic(s)
PWH=people with HIV
Q=quartile
RAL=raltegravir
RAM=resistance-associated mutation
RPV=rilpivirine
RTV=ritonavir
SAE=serious adverse event
STR=single-tablet regimen
SUBQ=subcutaneous
TAF=tenofovir alafenamide
TAM=thymidine analog mutation
TC=total cholesterol
TEAE=treatment-emergent adverse event
TG=triglycerides
TRAE=treatment-related adverse event
URTI=upper respiratory tract infection
VS=virologically suppressed

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