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Bixlenvo™ (bictegravir/lenacapavir) Use in Renal Impairment Not on Dialysis

This document is in response to your request for information regarding Bixlenvo™ (bictegravir/lenacapavir [BIC/LEN]) and use in individuals with renal impairment who are not on dialysis.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/BIXLENVO/BIXLENVO_pi.

Summary

Product Labeling[1]

No dosage adjustment of BIC/LEN is recommended in patients with mild, moderate or severe renal impairment (estimated CrCl ≥15 mL/min). BIC/LEN has not been studied in patients with ESRD (estimated CrCl <15 mL/min).

No clinically relevant differences in the pharmacokinetics of BIC were observed between participants with severe renal impairment (CrCl 15 to <30 mL/min, estimated by Cockcroft-Gault method) and participants with normal renal function. In a study of VS participants with ESRD (estimated CrCl <15 mL/min, by Cockcroft-Gault method) receiving chronic hemodialysis who were receiving a BIC-containing regimen, median BIC C_{trough} values were lower compared to participants with normal renal function. Despite significantly lower BIC C_{trough} values in this population, virologic suppression was maintained in this study.

There were no clinically significant differences in the pharmacokinetics of LEN in participants with severe renal impairment. The effect of ESRD (including dialysis) on the pharmacokinetics of LEN is unknown. As LEN is greater than 98.5% protein bound, dialysis is not expected to alter exposures of LEN.

Clinical Data on BIC/LEN Use in Renal Impairment

ARTISTRY-1: Participants with $eGFR_{CG}$ ≥15 mL/min who were not on renal replacement therapy were permitted in a phase 2/3 study that evaluated the safety and efficacy of switching to BIC/LEN vs continuing a complex ART regimen in VS PWH. During the phase 3 portion of the study, 1% of participants in the BIC/LEN arm had CrCl >15 to ≤30 mL/min and 15% of participants in the BIC/LEN arm had CrCl >30 to <60 mL/min. During the phase 2 and phase 3 portions of the study, 23% and 14%, respectively, of participants had a history of CKD. Outcomes were not reported separately for participants with CKD.[2,3]

ARTISTRY-2: Participants with $eGFR_{CG}$ ≥30 mL/min were permitted in a phase 3 study that evaluated the safety and efficacy of switching to BIC/LEN STR vs continuing BIC/FTC/TAF in VS PWH. At baseline, 5% and 6% of participants in the BIC/LEN and BIC/FTC/TAF

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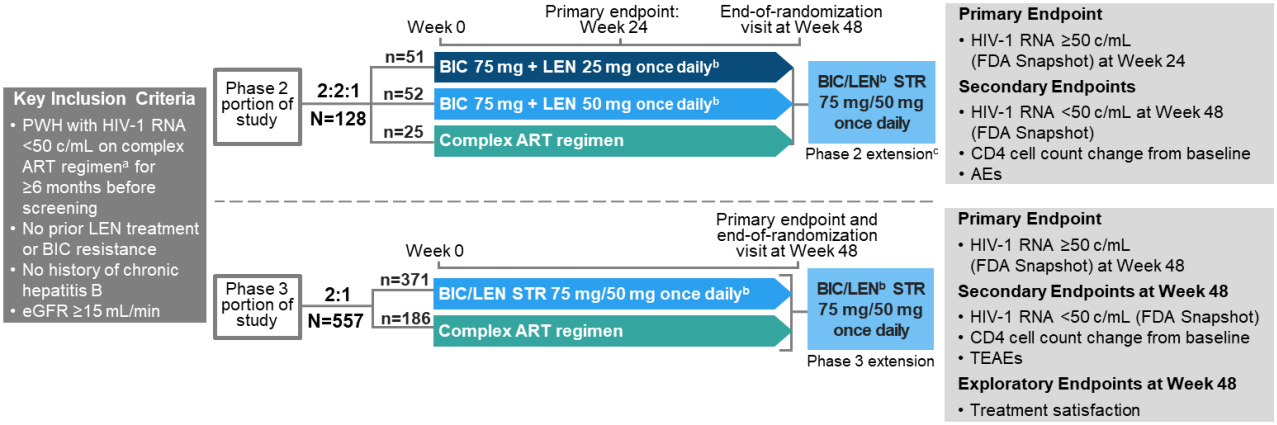
groups had CKD, respectively. Outcomes were not reported separately for participants with CKD.[4]

Clinical Data on BIC/LEN Use in Renal Impairment

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

ARTISTRY-1 is an ongoing, randomized, multicenter, open-label, phase 2/3 study (NCT05502341) evaluating the efficacy and safety of switching to BIC/LEN versus continuing a baseline complex ART regimen in VS PWH. Efficacy and safety outcomes were not reported separately for participants with CKD.[2,3]

Figure 1. ARTISTRY-1 Phase 2/3: Study Design[2,3,5-8]



[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]LEN oral loading doses (600 mg for 2 days) given after participants switched from their complex ART regimen.
[c]All participants reached Week 48 and completed 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 + LEN (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).[2,5]

Table 1. Phase 2 of ARTISTRY-1: Renal-related Baseline Characteristics[6]

Baseline Characteristic	BIC 75 mg + LEN 25 mg (n=51)	BIC 75 mg + LEN 50 mg (n=52)	Complex ART Regimen (n=25)
Age, years, median (range)	62 (26-79)	62 (34-76)	58 (41-70)
CKD[a], n (%)	12 (23.5)	14 (26.9)	5 (20.0)
$eGFR_{CG,a}$, mL/min, median (IQR)	80.4 (70.0, 99.5)	82.7 (65.4, 98.2)	81.2 (70.4, 102.1)

[a]Grouped terms in broad scope.

Switching to BIC 75 mg + LEN 50 mg demonstrated non-inferior efficacy compared with staying on a baseline complex ART regimen by FDA Snapshot analysis at the Week 24

primary endpoint (HIV-1 RNA ≥50 c/mL: 1.9% vs 0%, respectively; difference, 1.9%; 95% CI: -12.2% to 10.7%; P>0.99).[2]

TRAEs through Week 48 occurred in 17.6% (9/51) of participants in the BIC 75 mg + 25 mg group, 5.8% (3/52) of participants in the BIC 75 mg + 50 mg group, and none of the participants in the complex ART regimen group.[6] Two participants discontinued treatment due to TEAEs considered related to the study drugs through Week 48: one participant in the BIC 75 mg + LEN 25 mg group, due to grade 1 nausea and one participant in the BIC 75 mg + LEN 50 mg group with a history of nausea and vomiting, due to grade 3 worsening vomiting.[2,5]

At Week 24, Grade 3 or 4 renal-related laboratory abnormalities that occurred in ≥3 participants in any treatment group included low CrCl in participants with preexisting CKD (BIC 75 mg + LEN 25 mg, n=1 [2%]; BIC 75 mg + LEN 50 mg, n=6 [11.5%]; complex ART regimen, n=2 [12%]).[9] Laboratory abnormalities were not reported at Week 48.[5,6]

Phase 3 of ARTISTRY-1

For the phase 3 portion of the study, participants were randomly assigned (2:1) to receive BIC/LEN STR (n=371) or continue their stable complex ART regimen (n=186) for 48 weeks.

Table 2. Phase 3 of ARTISTRY-1: Renal-related Baseline Characteristics[3]

Baseline Characteristic	BIC/LEN 75 mg/50 mg (n=371)	Complex ART Regimen (n=186)
Age, years, median (range)	60 (22-84)	60 (24-75)
CKD[a], n (%)	49 (13)	29 (16)
CrCl, mL/min, median (IQR)	82.9 (66.4, 103.2)	82.4 (65.4, 100.2)
CrCl >15 to ≤30 mL/min, n (%)	3 (1)	3 (2)
CrCl >30-60 mL/min, n (%)	56 (15)	26 (14)
CrCl ≥60 mL/min, n (%)	312 (84)	157 (84)

[a]Grouped terms on standardized MedDRA query narrow search.

Switching to BIC/LEN demonstrated non-inferior efficacy compared with staying on a baseline complex ART regimen by FDA Snapshot analysis at the Week 48 primary endpoint (HIV-1 RNA ≥50 c/mL: 1% vs 1%, respectively; difference, -0.3%; 95.002% CI: -2.3% to 1.8%).[3]

Through Week 48, TRAEs were reported in 14% (53/371) of participants in the BIC/LEN group and 2% (3/186) of participants in the complex ART group. AEs leading to discontinuation of the study drug occurred in 2% (6/371) of participants in the BIC/LEN group and 1% (1/186) of participants in the complex ART group.[3] Refer to Table 3 for renal-related AEs by baseline eGFR and Table 4 for Grade ≥3 renal-related laboratory abnormalities through Week 48.[8]

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Table 3. Phase 3 of ARTISTRY-1: Renal-related Adverse Events Through Week 48 (Safety Analysis Set)[8]

Safety Outcome	eGFR >15 to ≤30 mL/min		eGFR >30 to <60 mL/min		eGFR ≥60 mL/min	
	BIC/LEN (n=3)	Complex ART Regimen (n=3)	BIC/LEN (n=56)	Complex ART Regimen (n=26)	BIC/LEN (n=312)	Complex ART Regimen (n=157)
Any Renal-related AE,[a] n (%)	0	1 (33)[b]	2 (4)[c]	7 (27)[d]	15 (5)[e]	7 (4)[f]

[a]Multiple AEs were counted once per participant for each preferred term. [b]Acute kidney injury. [c]Acute kidney injury (n=1), CKD (n=1). [d]CKD (n=3); acute kidney injury, hyperkalemia (n=2 each); pollakiuria, blood creatinine increased, toxic nephropathy (n=1 each). [e]Acute kidney injury, pollakiuria, hypokalemia, nocturia (n=2 each); CKD, hematuria, encephalopathy, GFR decreased, glycosuria, hypocalcemia, oliguria, proteinuria (n=1 each). [f]Renal CrCl decreased (n=2), acute kidney injury, CKD, blood Cr increased, hematuria, blood phosphate decreased, crystalluria, hypophosphatemia, pericarditis (n=1 each).

Table 4. Phase 3 of ARTISTRY-1: Renal-related Laboratory Abnormalities Through Week 48 (Safety Analysis Set)[8]

Grade ≥3 laboratory abnormalities occurring in ≥2% of participants in either group, n (%)	BIC/LEN 75 mg/50 mg (n=371)	Complex ART Regimen (n=183)
CrCl decreased	46 (12)	29 (16)
CrCl increased	11 (3)	11 (6)
Direct bilirubin level increased[a]	36 (10)	11 (6)

[a]All abnormalities Grade 3.

Age subgroup analysis[10,11]

In a subgroup analysis that assessed participant outcomes by age (<65 years and ≥65 years), a greater proportion of participants aged ≥65 years had lower baseline CrCl values than those aged <65 years. Among participants aged ≥65 years, 25% to 26% had a baseline CrCl of ≥30 to <60 mL/min and 0% to 3% had a baseline CrCl of ≥15 to <30 mL/min, compared with 8% to 10% and 0% to 1% of participants aged <65 years, respectively. CrCl remained stable among the majority of participants through Week 48, with only modest shifts between adjacent CrCl categories.

ARTISTRY-2: Switching to BIC/LEN vs BIC/FTC/TAF

ARTISTRY-2 is an ongoing, double-blind, multicenter, randomized, controlled, phase 3 study (NCT06333808) evaluating the efficacy and safety of switching to BIC/LEN (n=384) vs continuing BIC/FTC/TAF (n=193) in VS PWH.[4] Participants with $eGFR_{CG}$ ≥30 mL/min were permitted in the study.[12] At baseline, median age of participants was 49 years, and 5% (20/383) and 6% (12/191) of participants in the BIC/LEN and BIC/FTC/TAF groups had CKD, respectively. Efficacy and safety outcomes were not reported separately for participants with CKD.[4]

Switching to BIC/LEN demonstrated non-inferior efficacy compared with staying on a baseline regimen of BIC/FTC/TAF by FDA Snapshot analysis at the Week 48 primary endpoint (HIV-1 RNA ≥50 c/mL:1.3% vs 1.0%, respectively; difference, 0.3%; 95.002% CI: -1.9 to 2.4). Through Week 48, TRAEs occurred in 10% (40/383) and 12% (23/191) of participants in the BIC/LEN and BIC/FTC/TAF groups, respectively. TRAEs leading to

discontinuation of study drug occurred in 2 (<1%) and 1 (<1%) participants in the BIC/LEN and BIC/FTC/TAF groups, respectively.[4]

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Abbreviations

AE=adverse event
ART=antiretroviral therapy
ARV=antiretroviral
BIC=bictegravir
c/mL=copies/mL
CAD=coronary artery disease
CKD=chronic kidney disease
C_{trough}=trough concentration
DM=diabetes mellitus
DRV/RTV=darunavir/ritonavir
EFV=efavirenz
$eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault equation
FTC=emtricitabine
GFR=glomerular filtration rate
HTN=hypertension
LEN=lenacapavir
MedDRA=Medical Dictionary for Regulatory Activities
NI=non-inferiority
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OLE=open-label extension
PI=protease inhibitor
PWH=people with HIV-1
STR=single-tablet regimen
TAF=tenofovir alafenamide
TEAE=treatment-emergent adverse event
TRAE=treatment-related adverse event
URTI=upper respiratory tract infection
VS=virologically suppressed

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Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Bixlenvo US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/BIXLENVO/BIXLENVO_pi.

Follow-Up

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🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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