Lenacapavir (LEN)
Investigational Use with Islatravir

This document is in response to your request for information regarding lenacapavir (LEN) and its use in combination with the investigational agent islatravir (ISL) developed by Merck & Co., Inc., Kenilworth, NJ, USA.

Gilead Sciences, Inc. is providing this document to you, a US Healthcare Professional, in response to your unsolicited request for medical information. The information in this document is about an investigational regimen and the safety and efficacy has not been established for this combination. This document is not intended to offer an opinion regarding the safety and efficacy of this investigational regimen. The combination of ISL + LEN is investigational and has not been approved by U.S. Food & Drug Administration (FDA) or any other regulatory authority for use in patients.

Summary

Phase 3 Studies

- ISLEND-1 is a phase 3, randomized, double-blind, active-controlled study evaluating a switch to oral weekly ISL/LEN in PWH who are virologically suppressed on BIC/FTC/TAF.[1]
- ISLEND-2 is a phase 3, randomized, open-label, active-controlled study evaluating a switch to oral weekly ISL/LEN in PWH who are virologically suppressed on a standard of care antiretroviral regimen.[2]

Phase 2 Study

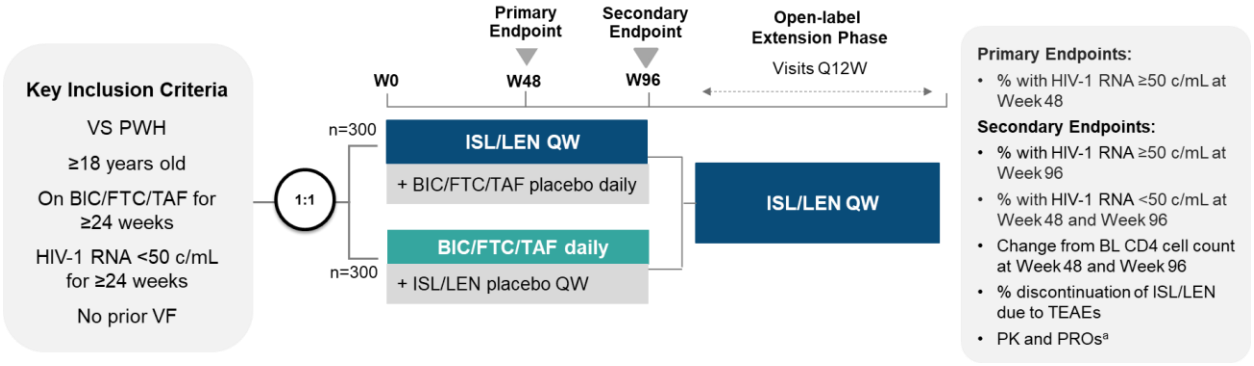
- Week 48 Results:
    - In virologically suppressed PWH, participants switching to oral ISL 2 mg weekly + oral LEN 300 mg weekly achieved a high rate of virologic suppression compared with remaining on BIC/FTC/TAF (94.2% vs 92.3%, respectively).[3,4]
- Week 96 Results:

  All enrolled PWH had the option to continue into the extension phase after 48 weeks. PWH were initially randomized to oral ISL+LEN (early switch) or PWH initially randomised to BIC/FTC/TAF before a switch to ISL+LEN (late switch)
    - All participants in the extension phase had HIV RNA ≤50 copies/mL at Week 96, including a participant with pre-existing M184V. Mean adherence to weekly oral ISL+LEN remained high in the early switch treatment group (99.3%) and in the late switch treatment group (98.6%). No emergent resistance to ISL or LEN was detected in either group. No treatment related Grade ≥3, serious AEs or AEs leading to study drug discontinuation were reported. No clinically significant changes in CD4+ T-cell or lymphocyte counts from baseline through Week 96 in either group. [5-7]

Phase 3 Studies

ISLEND-1 (NCT06630286) is a phase 3, randomized, double-blind, active-controlled study evaluating a switch to oral weekly ISL/LEN in PWH who are virologically suppressed on BIC/FTC/TAF (Figure 1).[1]

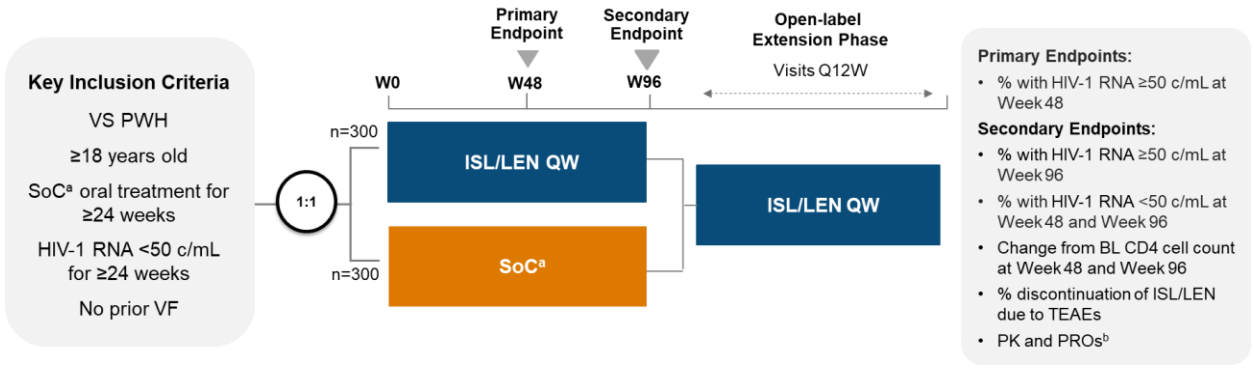
Figure 1. ISLEND-1 (NCT06630286) Study Design[1,8]



[a]PROs are an exploratory endpoint.

ISLEND-2 (NCT06630299) is a phase 3, randomized, open-label, active-controlled study evaluating a switch to oral weekly ISL/LEN in PWH who are virologically suppressed on a standard of care antiretroviral regimen (Figure 2).[2]

Figure 2. ISLEND-2 (NCT06630299) Study Design[2,8]



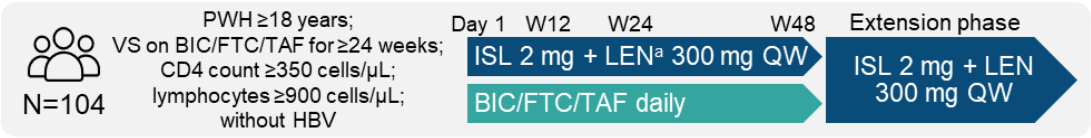
[a]SoC oral regimen: INSTI + 1 or 2 NRTIs, boosted PI + 2 NRTIs, or NNRTI + 2 NRTIs.
[b]PROs are an exploratory endpoint.

Study GS-US-563-6041 (NCT05052996)

Study Design and Demographics

Study GS-US-563-6041 (NCT05052996) is a phase 2, open-label, active-controlled clinical trial comparing switching to oral ISL 2 mg weekly + oral LEN 300 mg weekly or remaining on BIC/FTC/TAF daily in virologically suppressed PWH (Figure 3). The primary endpoint is the proportion of participants with HIV-1 RNA ≥50 copies/mL (c/mL) at Week 24 per FDA Snapshot algorithm.[9]

Figure 3. GS-US-563-6041 (NCT05052996) Study Design[3,9]



Outcomes

- **Primary:** HIV-1 RNA ≥50 c/mL (FDA Snapshot algorithm) at Week 24
- **Secondary:** HIV-1 RNA ≥50 c/mL at W48; HIV-1 RNA <50 c/mL at Week 48; change in CD4+ cell count; safety; PK

[a]600 mg LEN was given on Day 1 and Day 2 for pharmacologic loading.

Baseline demographics and disease characteristics are presented below (Table 1).

Table 1. Baseline Demographic and Disease Characteristics[9]

	Total (N=104)	ISL + LEN (n=52)	BIC/FTC/TAF (n=52)
Age, median (range), y	40 (26–76)	40 (28–67)	40 (26–76)
Female at birth, n (%)	19 (18.3)	10 (19.2)	9 (17.3)
Gender Identity, n (%)			
Transgender female	1 (1)	1 (1.9)	0
Non-binary/third gender	1 (1)	0	1 (1.9)
Race, n (%)			
White	52 (50)	25 (48.1)	27 (51.9)
Black	37 (35.6)	21 (40.4)	16 (30.8)
Asian	3 (2.9)	2 (3.8)	1 (1.9)
American Indian or Alaska Native	3 (2.9)	1 (1.9)	2 (3.8)
Native Hawaiian or Pacific Islander	1 (1)	0 (0)	1 (1.9)
Other	8 (7.7)	3 (5.8)	5 (9.6)
Ethnicity, Hispanic or Latinx, n (%)	30 (28.8)	13 (25.0)	17 (32.7)
CD4+ cells/µL, mean (SD)	786 (249.5)	755 (223.6)	818 (271.3)
≥500 cells/µL, n (%)	96 (92.3)	46 (88.5)	50 (96.2)
Lymphocytes x 10^3/µL, mean (SD)	1.94 (0.556)	1.94 (0.445)	1.95 (0.652)

Results

At Week 24, 94.2% of participants in both the ISL + LEN and BIC/FTC/TAF groups achieved HIV-1 RNA <50 c/mL. One (1.9%) participant in the ISL + LEN group had HIV-1 RNA ≥50 c/mL, but was later suppressed at Week 30. No participants in the BIC/FTC/TAF group had HIV-1 RNA ≥50 c/mL.[9]

At Week 48, 94.2% of participants in the ISL + LEN and 92.3% of BIC/FTC/TAF groups maintained HIV-1 RNA <50 c/mL. In the ISL+LEN group three participants discontinued (n=2 due to AEs not related to study drug and n=1 due to other reasons) and four participants in BIC/FTC/TAF discontinued (n=3 due to reasons not related to study drug and n=1 due to missing data but remained on study drug). All participants had HIV-1 RNA <50 c/mL at study discontinuation.[3]

At Week 48, no Grade ≥3 AEs, serious AEs, or AEs leading to study drug discontinuation were related to study drug.[3] No Grade 3 and 4 laboratory abnormalities were clinically significant, except ALT elevation seen in a participant with acute hepatitis B infection.[3]

There were no significant differences between groups in mean change from baseline in CD4+ cell or lymphocyte counts at Week 48. No participants discontinued due to CD4+ cell or lymphocyte count decreases.[3]

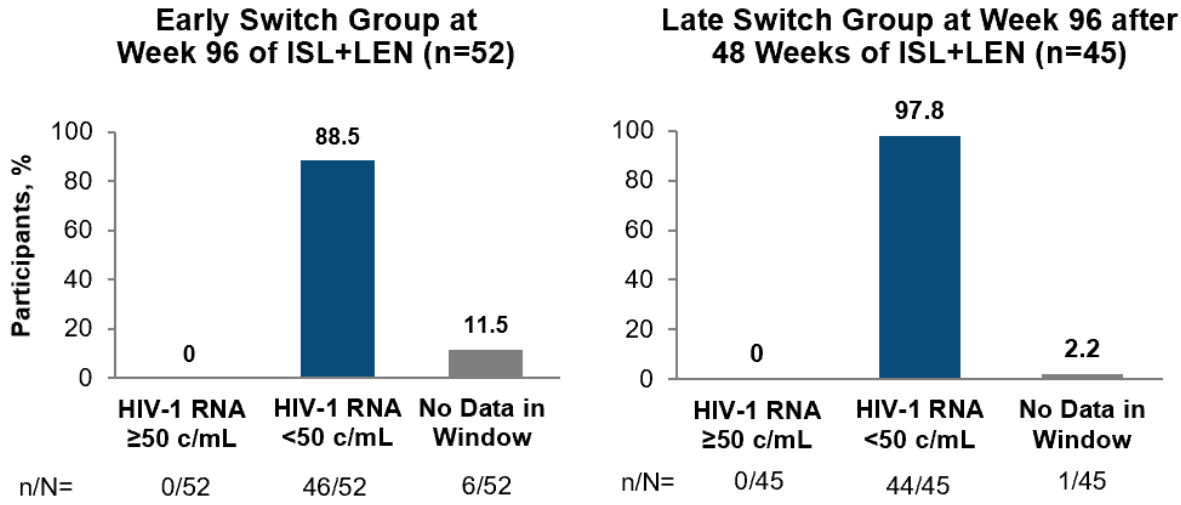
Week 96 Results

All enrolled participants had the option to continue into a 48-week extension phase. Participants randomized to the ISL+LEN continued for an additional 48 weeks (early switch group) and participants initially randomized to BIC/FTC/TAF switched to ISL + LEN (late switch group). Of the 52 participants who were randomized and treated with ISL+LEN in the randomized phase, 47 participants entered the extension phase in the late switch group of the 52 participants initially randomized to BIC/FTC/TAF 45 entered the extension phase.[5,6]

Baseline characteristics were similar between the two treatment groups; median age was 40 years, 18.6% were assigned female at birth and 50.5% were white in the combined population.[6]

At Week 96, all participants in both treatment groups with virologic data available had ≤50 copies/mL.(Figure 4.)[5,6]

Figure 4. Virologic Outcomes at Week 96[a6]



[a]106 participants were randomized; of the dosed participants (n=104), n=97 received ISL+LEN (early switch group: n=52; late switch group: n=45) and were included in the efficacy and safety analysis (in the late switch group, n=3 discontinued prior to Week 48; n=4 did not enter ISL+LEN extension phase at Week 48).

Mean adherence to weekly oral ISL+LEN remained high in the early switch treatment group (99.3%) and in the late switch treatment group (98.6%). Adherence was calculated by pill count. No virologic failure was observed. and no emergent resistance to ISL or LEN was detected.[5,6]

There were no treatment related Grade ≥3,serious AEs or AEs leading to study drug discontinuation related to ISL+LEN reported. (Table 2).[5,6]

Table 2 Adverse Events through Week 96[6]

Participants, n (%)	Early Switch Group (n=52)	Late Switch Group (n=45)	Total (N=97)
Any AE	46 (88.5)	35 (77.8)	81 (83.5)
TRAE	10 (19.2)	2 (4.4)	12 (12.4)
Grade 1 or 2 TRAE ≥2 participants in any group Dry mouth Nausea Fatigue	10 (19.2) 2 (3.8) 2 (3.8) 1 (1.9)	2 (4.4) 0 0 1 (2.2)	12 (12.4) 2 (2.1) 2 (2.1) 2 (2.1)
Grade ≥3 TRAE	0	0	0
SAE Treatment-related SAE	3 (5.8)[b] 0	0 0	3 (3.1) 0
AE leading to treatment discontinuation[a]	2 (3.8)[c]	0	2 (2.1)

aNot considered treatment related. bNeurologic anesthesia complication (n=1), renal colic/colon perforation in the same participant (n=1); pneumonia (n=1). cAcute HBV infection (n=1), renal colic/colon perforation in the same participant (n=1).

There were no clinically significant changes in CD4+ T-cell or lymphocyte counts from baseline through Week 96 in both groups, Body weight and BMI remained stable from baseline through Week 96 in both groups.[5,6]

Resistance Analysis at Week 96

An exploratory analysis of pre-existing HIV-1 resistance and post-baseline (on-treatment) resistance through Week 96 was conducted. Participants with primary NRTI or NNRTI resistance were not eligible for study enrollment; however, if participants were identified as having pre-existing NRTI or NNRTI resistance post-enrolment, they remained on study drug and were included in the analyses.[7]

Five participants based on historical genotype data were subsequently found to have primary RAMs affecting NRTIs or NNRTIs on screening genotype based on proviral sequencing they remained virologically suppressed at study Week 96, including two participants with pre-existing M184I/V reverse transcriptase mutations (n=1 per randomized group).[7] Two participants receiving ISL+LEN in the early switch group met criteria for post-baseline resistance analysis, neither of whom had baseline NRTI or NNRTI RAMs Both participants resuppressed on ISL+LEN without switching regimens, with no treatment-emergent resistance detected. No participants in the late switch group met criteria for resistance testing.[7]

Terms of Collaboration[10]

Under the terms of the agreement, Gilead and Merck will co-develop and co-commercialize long-acting products to treat people living with HIV that combine Gilead's lenacapavir and Merck's proprietary investigational nucleoside reverse transcriptase translocation inhibitor, islatravir. The collaboration will initially focus on long-acting oral formulations and long-

acting injectable formulations of these combination products, with other formulations potentially added to the collaboration as mutually agreed.

References

1. National Institutes of Health (NIH). Study to Compare an Oral Weekly Islatravir/ Lenacapavir Regimen With Bictegravir/ Emtricitabine/ Tenofovir Alafenamide in Virologically Suppressed People With HIV-1 (ISLEND-1). Available at: https://clinicaltrials.gov/study/NCT06630286. Accessed: 09 April 2026. Last Updated: 13 November. 2025.
2. National Institutes of Health (NIH). Study to Compare an Oral Weekly Islatravir/ Lenacapavir Regimen With Standard of Care in Virologically Suppressed People With HIV-1 (ISLEND-2). Available at: https://clinicaltrials.gov/study/NCT06630299. Accessed: 09 April 2026. Last Updated: 14 November. 2025.
3. Colson AE, Crofoot GE, Ruane PJ, et al. Week 48 Results of a Phase 2 Study Evaluating Once-weekly Oral Islatravir Plus Lenacapavir [Presentation 577]. Paper presented at: IDWeek; October 16-19, 2024; Los Angeles, California.
4. VanderVeen LA, Chang S, Selzer L, et al. Resistance Analysis of Weekly Islatravir Plus Lenacapavir in People With HIV at 48 Weeks. [Poster #736]. Paper presented at: Conference on Retroviruses and Opportunistic Infections; March 09–12, 2025; San Francisco, CA.
5. Colson AE, Crofoot GE, Ruane PJ, et al. Oral Weekly Islatravir Plus Lenacapavir in Virologically Suppressed People with HIV-1: 96 Week Outcomes from a Phase 2 Study. [Presentation #PS15.5.LB]. Paper presented at: The 20th European AIDS Conference; October 15-18, 2025; Paris, France.
6. Colson AE, Crofoot GE, Ruane PJ, et al. Once-Weekly Islatravir Plus Lenacapavir Mantains HIV-1 Suppression Through 96 Weeks: Phase 2 Study [Poster #516]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25, 2026; Denver, CO.
7. Beckerman E, Chang S, Diamond TL, et al. Resistance Analysis of Weekly Islatravir Plus Lenacapavir in People with HIV at 96 Weeks. [Poster #586]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25, 2026; Denver, CO.
8. Gilead Sciences Inc. Data on File.
9. Colson AE, Crofoot GE, Ruane PJ, et al. Efficacy and Safety of Weekly Islatravir Plus Lenacapavir in PWH at 24 Weeks: A Phase 2 Study.[Presentation Oral-14]. Paper presented at: 31st Conference on Retroviruses and Opportunistic Infections (CROI),; March 3-6, 2024; Denver, Colorado.
10. Gilead and Merck announce agreement to jointly develop and commercialize long-acting, investigational treatment combinations of Lenacapavir and Islatravir in HIV [Press Release]. 15 March [press release]. 2021.

Abbreviations

BIC=bictegravir
BL=baseline
c/mL=copies/mL
FTC=emtricitabine
GLSM=geometric least squares mean
INSTI-R=
ISL=islatravir
LEN=lenacapavir
NNRTI=non-nucleoside reverse transcriptase inhibitor
NNRTI-R=NNRTI resistance
NRTI=nucleoside reverse transcriptase inhibitor
NRTI-R=NRTI resistance
PI-R=protease inhibitor resistance
PK=pharmacokinetic(s)
PRO=patient-reported outcome
PWH=people with HIV
Q12W=every 12 weeks
QW=every week
RT=reverse transcriptase
SoC=standard of care
TAF=tenofovir alafenamide
TEAE=treatment-emergent adverse event
TRAE=treatment related adverse event
VF=virologic failure
VS=virologically suppressed
W=week

Follow Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
https://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

Data Privacy

The Medical Information service at Gilead Sciences may collect, store and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact gilead.privacy@gilead.com.