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]

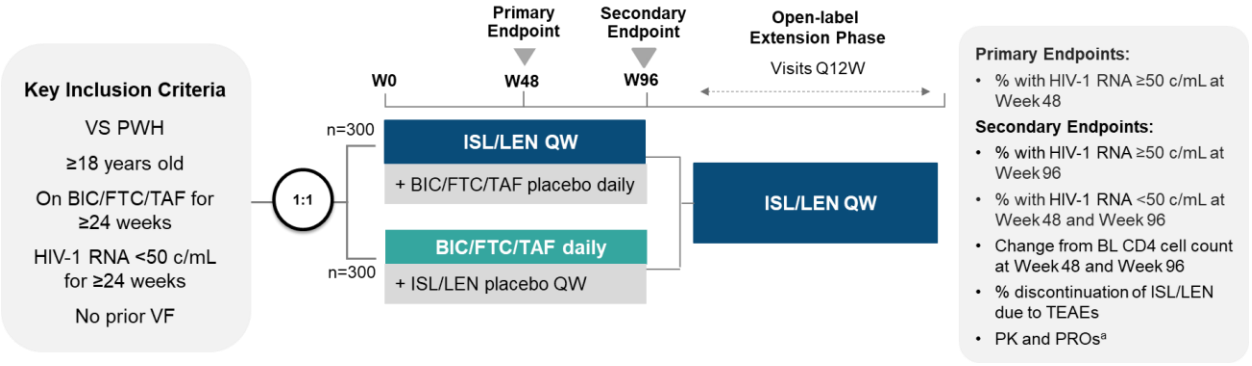
Phase 2 Study

- 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). No participants in the study developed treatment-emergent HIV-1 drug resistance. No Grade ≥3 adverse events, serious adverse events, or adverse events leading to study drug discontinuation were related to study drug. There were no significant differences between groups in mean change from baseline in CD4+ cell or lymphocyte counts.[3,4]
- Week 96 Results:
    - PWH initially randomized to oral ISL+LEN had the option to continue into the extension phase after 48 weeks. All participants in the extension phase had HIV RNA ≤50 copies/mL at Week 96. Mean adherence to weekly oral ISL+LEN remained high (99.3%) and no emergent resistance to ISL or LEN was detected. No treatment related Grade≥3 or serious AEs were reported. No clinically significant changes in CD4+ T-cell or lymphocyte counts from baseline through Week 96. [5]

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]

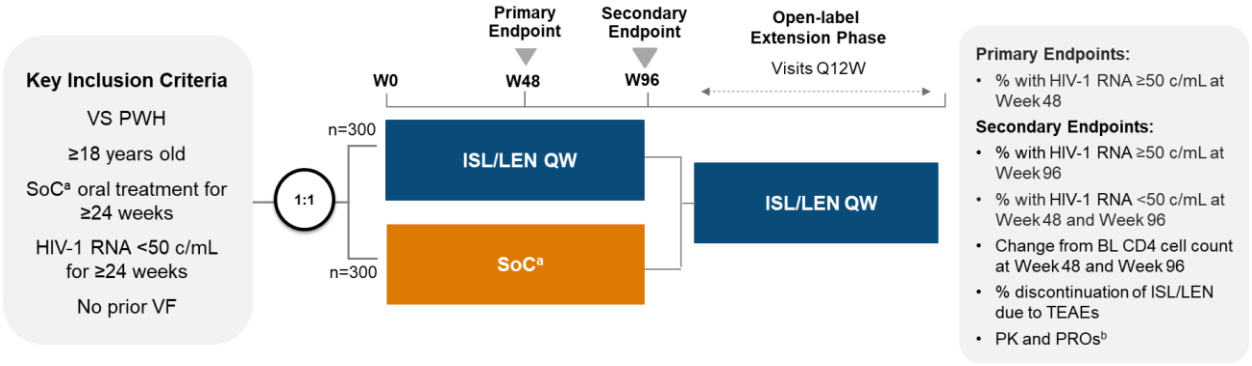
Figure 1. ISLEND-1 (NCT06630286) Study Design[1,6]



[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[2,6]



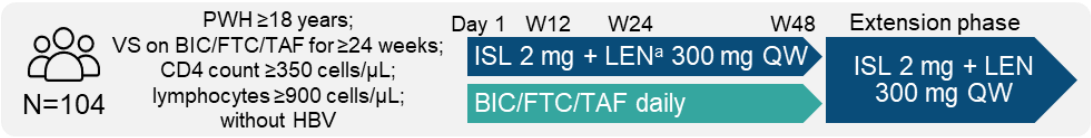
[a]SoC oral regimen: INSTI + 1 or 2 NRTIs, boosted PI + 2 NRTIs, or NNRTI + 2 NRTIs.
[b]PROs are an exploratory endpoint.

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.[7]

Figure 3. GS-US-563-6041 (NCT05052996) Study Design[3,7]



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[7]

	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.[7]

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]

An exploratory resistance analysis of pre-existing HIV-1 resistance at baseline and post-baseline (on-treatment) resistance through Week 48 was conducted. At baseline, pre-existing primary resistance-associated mutations detected in the total study population were low: NRTI-R, n=4 (3.8%); NNRTI-R, n=2 (1.9%); PI-R, n=6 (5.8%); INSTI-R, n=2 (2.0%). These rates were similar between treatment arms.[4]

Of the participants who were virologically suppressed at Week 48, 2 participants had pre-existing M184V/I in RT (n=1 per group).[4]

One participant in the ISL + LEN group who had no pre-existing NRTI or NNRTI RAMs was viremic at Day 1 (HIV-1 RNA=251 c/mL) met criteria for post-baseline resistance analysis. No treatment-emergent resistance was detected and the participant achieved sustained viral suppression after Week 36 while staying on ISL + LEN.[4]

One participant in each study arm had M184V/I primary resistance substitution at baseline. All participants with pre-existing NRTI-R or NNRTI-R in both study arms were virologically suppressed at Week 48, including the two participants with pre-existing M184V/I in RT (n=1 per group). No participants in the study developed treatment-emergency HIV-1 drug resistance.[4]

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]

Patient-Reported Outcomes Results at Week 48[8]

An analysis was conducted to assess PRO (Patient-Reported Outcome) data from the study at Week 48, treatment satisfaction and Quality of Life were assessed at baseline through 48 Weeks in both arms.

PRO tools included:

- HIV Treatment Satisfaction Questionnaire (HIVTSQs): a 12-item validated instrument designed to measure treatment satisfaction.
- HIV Patient Perspective of Regimen Change and HIV Patient Perspective of Regimen: novel, content-valid, 10-item questionnaires assessing perception of the current trial HIV-1 regimen and switch to long-acting therapy
- EQ-5D Visual Analogue Scale: measures perceived overall health status, with the score ranging from the worst possible health status to the best possible health status.[8]

At 48 weeks, numerically more participants receiving once-weekly oral ISL+LEN reported improved regimen fit into their lifestyle, reduced reminder of HIV status and less worry about taking pills than those receiving once-daily B/F/TAF

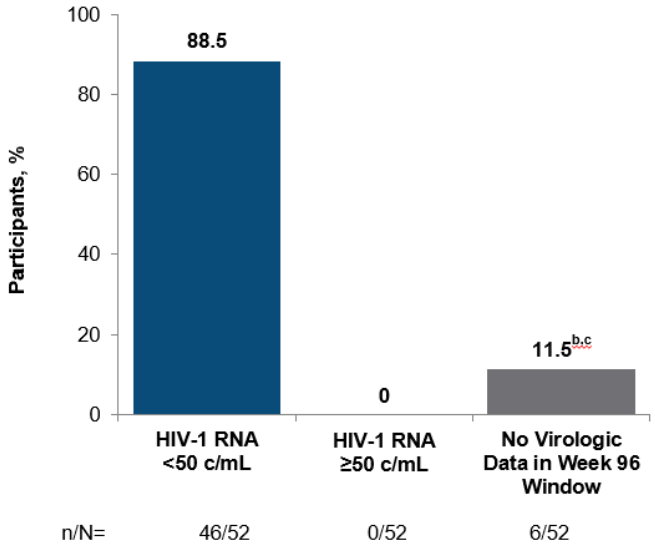
- 65.4% of participants receiving once-weekly oral ISL+LEN reported their prior regimen was more burdensome
- 69.2% of participants were more/much more satisfied with once-weekly oral ISL+LEN than the once-daily regimen
- Perception of health status was similar for participants receiving QW oral ISL+LEN and QD oral B/F/TAF[8]

Week 96 Results

Participants randomized to the ISL+LEN had the option to continue into a 48 week extension phase. Of the 52 participants who were randomized and treated with ISL+LEN in the randomized phase, 47 participants entered the extension phase, 1 participant discontinued the study (participant's decision) during the extension phase.[5]

At Week 96, all participants in the extension phase (n=46) and participants who discontinued study drug during the extension phase (n=6) had HIV RNA ≤50 copies/mL. (Figure 4).[5]

Figure 4. Virologic Outcomes at Week 96[a5]



[a]Missing=failure analysis.
[b]6 participants with no data in window: n=2 discontinued due to unrelated AEs prior to Week 48 (n=1 large intestine perforation and renal colic; n=1 acute hepatitis B), n=2 discontinued due to personal reasons and n=2 completed 48 weeks of the randomized phase and chose not to enter the extension phase due to personal reasons.
[c]All participants had HIV-1 RNA <50 c/mL at study discontinuation.

No virologic failure was observed. Mean adherence to weekly oral ISL+LEN remained high (99.3%) and no emergent resistance to ISL or LEN was detected.[5]

There were no treatment related Grade ≥3 or serious AEs reported (Table 2)[5]

Table 2. Adverse Events through Week 96[5]

Participants, n (%)	ISL + LEN (n=52)
Any AEs	46 (88.5)
Treatment-related AEs	10 (19.2)
Grade 1 and 2	10 (19.2)
Occurring in ≥2 participants	
Dry mouth	2 (3.8)
Nausea	2 (3.8)
Grade ≥3	0
Serious AE	3 (5.8)
Treatment related	0
AE leading to study drug discontinuation	2 (3.8)
Treatment related	0

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

Terms of Collaboration[9]

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: Accessed: 27 January 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: Accessed: 27 January 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. Gilead Sciences Inc. Data on File.
7. 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.
8. Eron J, Colson AE, Ramgopal MN, et al. Patient-Reported Outcomes From People With HIV-1 Receiving Once-Weekly Oral Islatravir in Combination With Lenacapavir: Phase 2 Week 48 Results [Poster #eP133]. Paper presented at: The 20th European AIDS Conference; October 15-18, 2025; Paris, France.
9. 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

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