GILEAD | Medical Information

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. This regimen has not been approved by U.S. Food & Drug Administration (FDA) or any other regulatory authority for use in patients.

Summary

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-emergency 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.[1,2]

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.[3]
- 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.[4]

Additional Studies

- In a phase 1 study in healthy participants to evaluate the pharmacokinetics (PK), safety, and tolerability of oral ISL 20 mg and oral LEN 600 mg administered alone or in combination, PK data indicated no significant drug-drug interactions for the coadministration of oral ISL + oral LEN, and coadministration was generally well tolerated.[5]
- In an ISL population PK model, ISL 2 mg weekly is predicted to rapidly achieve efficacious exposures for wild-type and M184I/V HIV variants and have similar CD4+ T cell and lymphocyte increases as standard antiretroviral therapy for PLWH who are virologically suppressed.[6]

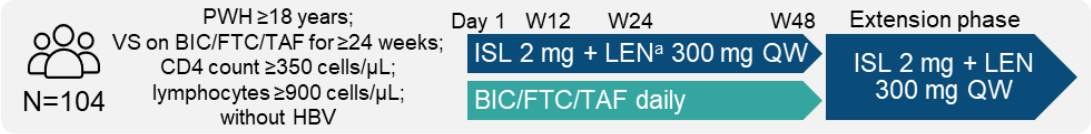
- Several in vitro studies were conducted to assess the antiretroviral activity of ISL with LEN. ISL + LEN demonstrated additive inhibition of HIV-1 replication with no antagonism or cross-resistance observed between ISL and LEN.[7]

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 1). The primary endpoint is the proportion of participants with HIV-1 RNA ≥50 copies/mL (c/mL) at Week 24 per FDA Snapshot algorithm.[8]

Figure 1. GS-US-563-6041 (NCT05052996) Study Design[1,8]



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[8]

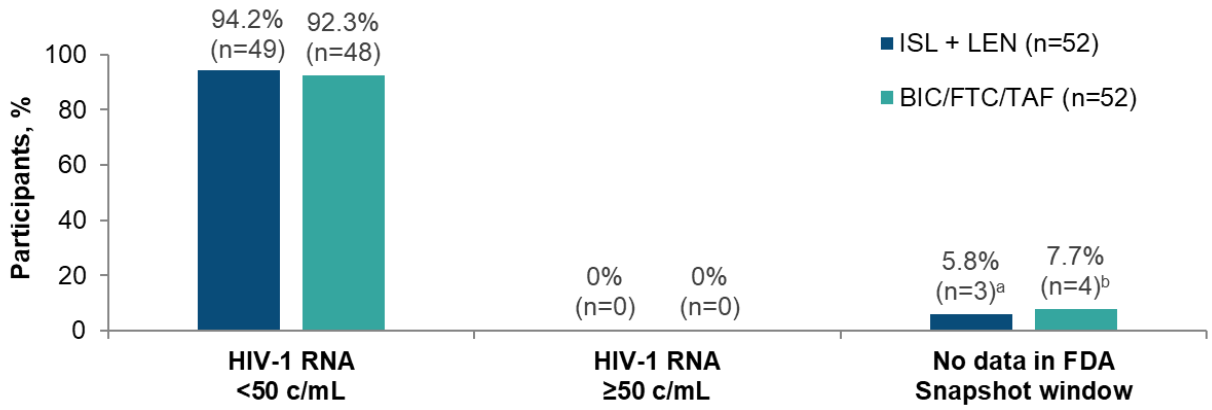
	Total (N=104)	ISL + LEN (n=52)	BIC/FTC/TAF (n=52)
Age, median (range), y	40 (26–76)	40 (28–67)	40 (26–76)
Female at birth, n (%)	19 (18.3)	10 (19.2)	9 (17.3)
Gender Identity, n (%)			
Transgender female	1 (1)	1 (1.9)	0
Non-binary/third gender	1 (1)	0	1 (1.9)
Race, n (%)			
White	52 (50)	25 (48.1)	27 (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.[8]

At Week 48, participants in both treatment groups maintained high rates of virologic suppression (Figure 2).[1]

Figure 2. Virologic Outcomes at Week 48[1]



[a]Discontinued due to AEs not related to study drug, n=2; discontinued due to other reasons not related to study drug, n=1. All participants had HIV-1 RNA <50 c/mL at study discontinuation.
[b]Discontinued due to other reasons not related to study drug and had HIV-1 RNA <50 c/mL at study discontinuation, n=3; missing data during window but remained on study drug, n=1.

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.[2]

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

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.[2]

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.[2]

At Week 48, no Grade ≥3 AEs, serious AEs, or AEs leading to study drug discontinuation were related to study drug (Table 3).[1]

Table 3. Adverse Events through Week 48[1]

Participants, n (%)	ISL + LEN (n=52)	BIC/FTC/TAF (n=52)
Any AE	42 (80.8)	40 (76.9)
Treatment-related AEs	10 (19.2)	3 (5.8)
Grade 1 and 2 (≥2 ISL + LEN participants)	10 (19.2)	3 (5.8)
Dry mouth	2 (3.8)	0
Nausea	2 (3.8)	0
Grade 3 and 4	0	0
Serious AE	3 (5.8)[a]	0
Treatment-related	0	0
AE leading to study drug discontinuation	2 (3.8)[b]	0
Treatment-related	0	0

[a]Serious AEs included large intestine perforation and renal colic (in the same participant), pneumonia, and neurologic anesthetic complication.
[b]Large intestine perforation and renal colic, n=1; acute hepatitis B infection, n=1 (both participants had HIV-1 RNA <50 c/mL at study discontinuation).

No Grade 3 and 4 laboratory abnormalities were clinically significant, except ALT elevation seen in a participant with acute hepatitis B infection (Table 4).[1]

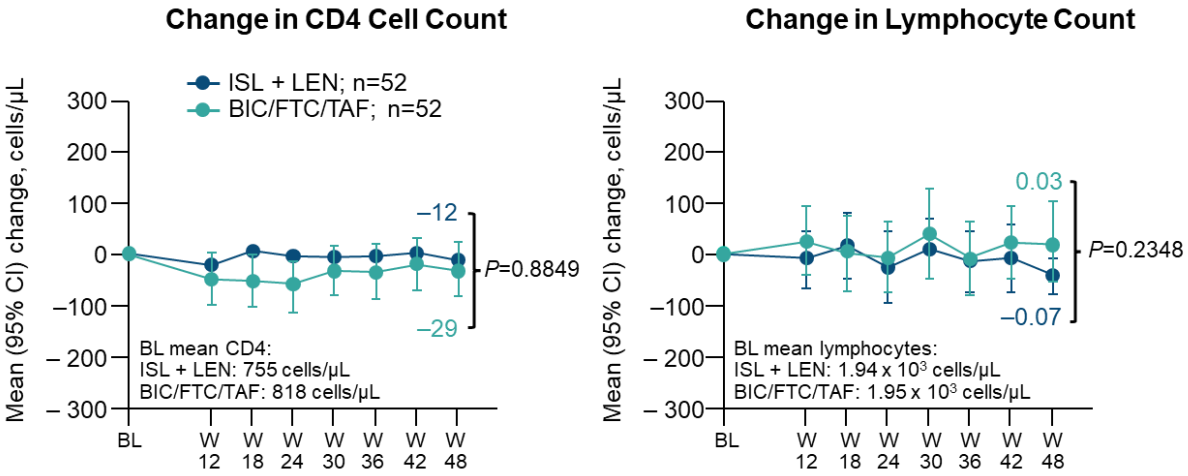
Table 4. Laboratory Abnormalities through Week 48[1]

Laboratory abnormalities occurring in ≥1 participant in the ISL + LEN group, n (%)	ISL + LEN (n=52)	BIC/FTC/TAF (n=52)
Grade 3		
Creatinine (increased)	1/52 (1.9)	0/51
Creatinine clearance (decreased)	2/52 (3.8)	2/51 (3.9)
Non-fasting hyperglycemia	1/43 (2.3)	2/43 (4.7)
Glycosuria	1/52 (1.9)	2/51 (3.9)
Hyperkalemia	1/52 (1.9)	0/51
ALT (increased)[a]	1/52 (1.9)	0/51
Grade 4		
Creatine kinase (increased)[b]	2/52 (3.8)	0/51

[a]Increased ALT occurred in participant with acute hepatitis B infection.
[b]Increased creatinine kinase occurred after vigorous exercise in both participants.

There were no significant differences between groups in mean change from baseline in CD4+ cell or lymphocyte counts at Week 48 (Figure 3). No participants discontinued due to CD4+ cell or lymphocyte count decreases.[1]

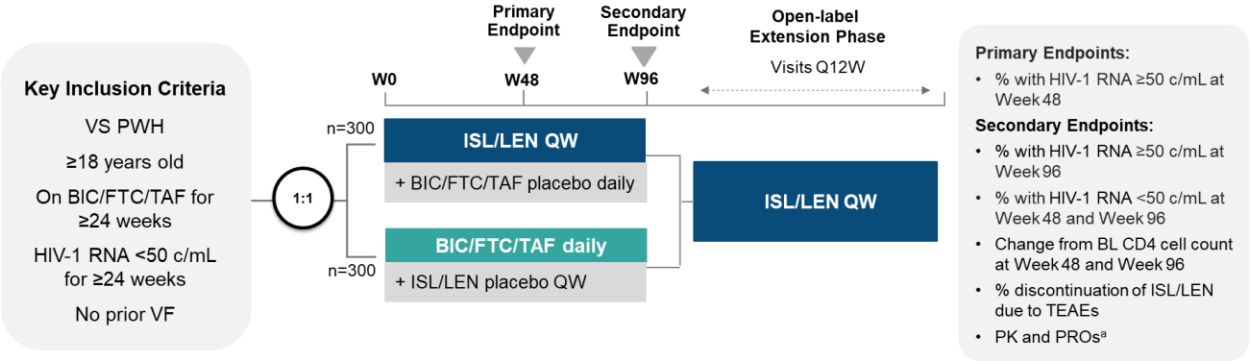
Figure 3. CD4 and Lymphocytes Through Week 48[1]



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 4).[3]

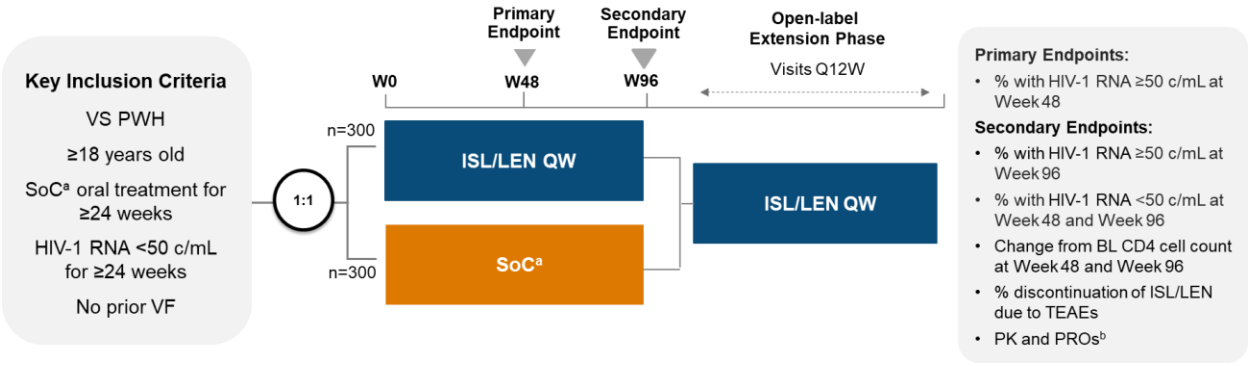
Figure 4. ISLEND-1 (NCT06630286) Study Design[3,9]



[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 5).[4]

Figure 5. ISLEND-2 (NCT06630299) Study Design[4,9]



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

Phase 1 Long-Acting Oral Studies

Separate phase 1 studies were completed for oral ISL[10] and oral LEN[11] as single agents.

Evaluation of Potential Drug-Drug Interactions Between Oral ISL and Oral LEN

Study Design and Baseline Demographics

A phase 1, open-label, parallel-design, single-dose, three-cohort study (GS-US-563-6148) in 55 healthy participants was conducted to evaluate the pharmacokinetics (PK), safety, and tolerability of oral ISL 20 mg and oral LEN 600 mg administered alone or in combination. Participants received single oral doses of coadministered oral ISL 20 mg and oral LEN 600 mg (n=18), oral ISL 20 mg only (reference: n=18), or oral LEN 600 mg only (reference: n=19). Fifteen (15), evaluable participants per cohort with 20% overage were enrolled for ≥90% power with no-effect boundaries of 60-167%, assuming a coefficient of variation of 41.4%, based on ISL area under the curve from a previous study. Plasma PK samples were collected up to Day 12 for oral ISL and Day 43 for oral LEN. Baseline characteristics were comparable between groups. Most participants were white, male at birth, and mean age was 32-35 years.[5]

Results

PK data indicated no significant drug-drug interactions for the coadministration of oral ISL and oral LEN. The PK of oral ISL and oral LEN were similar when comparing administration alone or in combination based on point estimates of % GLSM ratios and 90% CIs (Table 5).[5]

Table 5. PK Parameter Estimates and Comparisons[5]

	Mean PK Parameter (%CV)	ISL + LEN (n=18)	Reference*: ISL Only (n=16) or LEN Only (n=18)	ISL + LEN vs Reference % GLSM Ratio (90% CI)
ISL	C_{max}, ng/mL	145 (41.3)	165 (42.2)	87.9 (68.7, 113)
	AUC_{inf}, h·ng/mL	674 (25.4)	642 (25.8)	105 (90.2, 123)
	T_{max}, median (min, max), h	0.75 (0.50, 2.00)	0.75 (0.50, 2.00)	-
	Apparent terminal $t_{1/2}$, h	121 (18.7)	99.1 (14.6)	-
LEN	C_{max}, ng/mL	33.7 (77.7)	37.9 (57.0)	80.1 (50.9, 126)
	AUC_{inf}, h·ng/mL	9840 (51.0)	10,800 (56.9)	88.6 (60.5, 130)
	T_{max}, median (min, max), h	8.00 (1.00, 48.0)	10.0 (2.00, 312)	-
	Apparent terminal $t_{1/2}$, h	296 (23.5)	308 (24.7)	-

AUC_{inf}=area under the curve from 0 to infinity; C_{max}=maximum concentration; T_{max}=time to C_{max}; $t_{1/2}$=half-life.
*PK analysis was performed for 16 participants in the ISL only cohort and for 18 in the LEN only cohort due to important protocol deviations.

Coadministration of single dose oral ISL 20 mg and oral LEN 600 mg was generally well tolerated. There were no serious, or Grade 3 or 4 adverse events, and no clinically relevant Grade 3 or 4 laboratory abnormalities were observed.[5] CD4+ T-cells were not assessed as part of routine monitoring in this healthy participant study.[9]

Additional Studies

No Antagonism or Cross-Resistance Observed Between ISL + LEN

Several in vitro studies were conducted to assess the antiviral activity of ISL with LEN which support the combination of ISL and LEN for the treatment of HIV-1 infection.[7]

Results

ISL + LEN demonstrated additive inhibition of HIV-1 replication. No antagonism or cross-resistance was observed between ISL and LEN. ISL + LEN more effectively suppressed viral breakthrough and demonstrated a higher barrier of emergence of resistance than either compound on its own.[7]

Modeling of ISL Weekly Dose in Virologically Suppressed PWH

Study Design

An ISL population PK model was developed incorporating ISL PK data from once daily and weekly doses. Subsequently an ISL population PKPD model was developed incorporating longitudinal CD4+ T-cell and lymphocyte data from long-term ISL studies. These PK/PD model predictions were compared to CD4+ T cell changes of approved antiretroviral therapy regimens for PLWH who are virologically suppressed. Revised ISL weekly doses were selected based on simulated doses providing ISL exposures ensuring coverage for wild-type and M184I/V variants as well as CD4+ T cell and total lymphocyte changes comparable to standard antiretroviral therapies in switch population.[6]

Results

ISL 2 mg weekly is predicted to rapidly achieve efficacious exposures for wild-type and M184I/V HIV variants and have similar CD4+ T cell and lymphocyte increases as standard antiretroviral therapy for PLWH who are virologically suppressed.[6]

Terms of Collaboration[12]

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

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3. 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: 25 October 2024. Last Updated: 08 October. 2024.
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5. Zhang H, Mortensen E, Rhee M, et al. Evaluation of Potential Drug-Drug Interactions Between Islatravir and Lenacapavir [Poster 433]. Paper presented at: Virtual Conference on Retroviruses and Opportunistic Infections (CROI) 2022; 12-16 February, 2022.
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9. Gilead Sciences Inc. Data on File.
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12. 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 Pharmacovigilance and Epidemiology ☎ 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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