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Lenacapavir (LEN) Investigational Use With Islatravir

This document is in response to your request for information regarding clinical study data on 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 of these treatments when used in combination has not been established. This document is not intended to offer an opinion regarding the safety and efficacy of this investigational regimen. The use of ISL + LEN for the treatment of HIV-1 is investigational and is not approved by the US FDA or any other regulatory authority for use in patients.

Summary

Phase 3 Clinical Studies on the Use of LEN and ISL

ISLEND-1 is an ongoing phase 3, randomized, double-blind, active-controlled study evaluating a switch to oral once-weekly ISL/LEN STR in PWH who were VS on BIC/FTC/TAF.[1]

- At Week 48, high rates of virologic suppression were maintained, with 0% in the ISL/LEN group and 0.3% in the BIC/FTC/TAF group with HIV-1 RNA ≥50 c/mL (treatment difference, 0.3%; 95.002% CI: -1.4 to 0.8%).
- In the ISL/LEN group, no participants developed resistance to either component, and rates of virologic suppression were similar between those with and without M184V/I at baseline.
- Most AEs and TRAEs were Grade 1 or 2 in severity. Discontinuations due to AEs occurred in 2% and 1.7% of participants in the ISL/LEN and BIC/FTC/TAF groups, respectively.

ISLEND-2 is a phase 3, randomized, open-label, active-controlled study evaluating a switch to oral once-weekly ISL/LEN STR in PWH who were VS on an SOC ARV regimen.[2]

- At Week 48, high rates of virologic suppression were noted, with 0.3% in the ISL/LEN group and 1.3% in the SOC group with HIV-1 RNA ≥50 c/mL (treatment difference, -1%; 95.002% CI: -3 to 1.1%).
- In the ISL/LEN group, no participants developed resistance to either component.
- No Grade ≥3 TRAEs occurred in either group; 1 treatment-related SAE occurred in the ISL/LEN group, and none occurred in the SOC group. Discontinuations due to AEs occurred in 7% and 9% of participants in the ISL/LEN and SOC groups, respectively.

Phase 2 Clinical Studies on the Use of LEN and ISL

Study GS-US-563-6041, a phase 2, open-label, active-controlled clinical trial, evaluated switching to oral once-weekly doses of ISL 2 mg + LEN 300 mg or remaining on BIC/FTC/TAF daily in VS PWH. The study was not powered for analysis.[3]

- With ISL + LEN and BIC/FTC/TAF treatment, virologic suppression was maintained at Week 24 (HIV-1 RNA ≥50 c/mL: 1.9% vs 0%, respectively; treatment difference of 1.9%; 95% CI: -5.2 to 10.5%) and Week 48 (0% vs 0%).[3]
- All enrolled PWH had the option to continue into the OLE phase after 48 weeks. The early switch group consisted of participants initially randomized to oral ISL + LEN, and the late switch group comprised those initially randomized to BIC/FTC/TAF before switching to ISL + LEN.[4,5]
  - All participants in the OLE phase had HIV RNA ≤50 c/mL at Week 96, including a participant with preexisting M184V.[6]
  - No treatment-emergent resistance to ISL or LEN was detected in either group.[4,5]
  - No treatment-related Grade ≥3 AEs, SAEs, or AEs that led to study drug discontinuation were reported.[4-6]

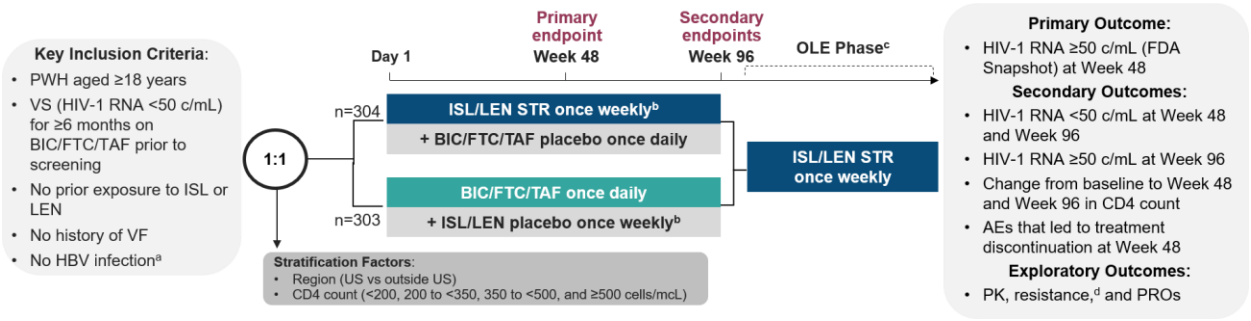
Phase 3 Clinical Studies on the Use of LEN and ISL

ISLEND-1 Study

Study design and demographics[1,7]

ISLEND-1 (NCT06630286) is an ongoing, phase 3, randomized, double-blind, active-controlled, noninferiority study comparing efficacy and safety outcomes between VS PWH treated with BIC/FTC/TAF who switched to once-weekly oral ISL/LEN or remained on once-daily oral BIC/FTC/TAF (Figure 1). The primary endpoint is the proportion of participants with HIV-1 RNA ≥50 c/mL at Week 48 per FDA Snapshot algorithm (noninferiority margin, 4%).

Figure 1. ISLEND-1: Study Design[1,7,8]



[a]Not positive for HBsAg or not positive for HBcAb and negative for HBsAb.
[b]Loading dose: 2 tablets of ISL/LEN (each containing 0.5 mg ISL and 300 mg LEN) on Days 1 and 2. Matching ISL/LEN placebo loading dose strategy was used in the BIC/FTC/TAF group. Maintenance dose: 1 tablet (containing 2 mg ISL and 300 LEN) once weekly starting on Day 8; matching ISL/LEN placebo was used in the BIC/FTC/TAF group. Both treatments were administered with or without food.
[c]Open-label ISL/LEN to continue until it becomes commercially available or the study is discontinued, whichever comes first.
[d]Treatment-emergent resistance testing performed for participants with confirmed VF (HIV-1 RNA >50 c/mL at any timepoint post-baseline or at the last visit on-treatment); genotypic and phenotypic testing was performed for those with HIV-1 RNA ≥200 c/mL.

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

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Table 1. ISLEND-1: Baseline Demographics and Disease Characteristics[1]

Key Demographics and Characteristics		Total (N=307)	ISL/LEN (n=304)	BIC/FTC/TAF (n=303)
Age, median (IQR), years		49 (38–60)	49 (38–60)	48 (38–60)
Assigned female sex at birth, n (%)		125 (20.6)	67 (22)	58 (19.1)
Race,[a] n (%)	White	276 (45.5)	148 (48.7)	128 (42.2)
	Black	189 (31.1)	89 (29.3)	100 (33)
	Asian	65 (10.7)	32 (10.5)	33 (10.9)
Ethnicity,[a] Hispanic or Latinx, n (%)		160 (26.4)	73 (24)	87 (28.7)
CD4, mean ± SD, cells/mcL		742±304.4	739±289.2	745±319.3
<200 cells/mcL, n (%)		9 (1.5)	3 (1)	6 (2)
Absolute lymphocytes, mean ± SD, cells/mcL		1880±572	1860±524	1900±617[b]

[a]These data were reported by the participants. [b]Data were not available for 1 participant.

Week 48 results

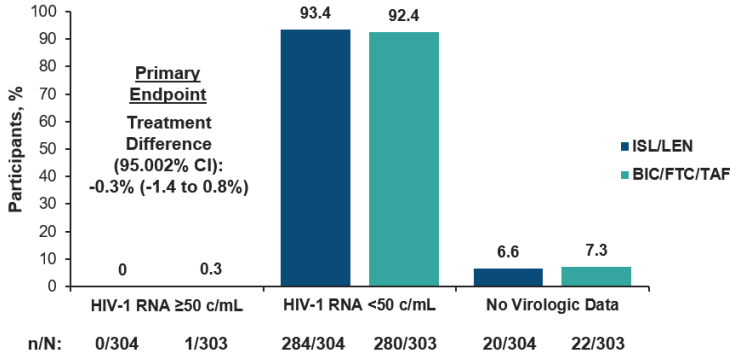
Efficacy[1]

The primary analysis included 304 participants in the ISL/LEN group and 303 in the BIC/FTC/TAF group; 283 and 279 participants, respectively, continued their assigned treatment after Week 48.

At Week 48, ISL/LEN demonstrated noninferior efficacy compared with staying on BIC/FTC/TAF (HIV-1 RNA ≥50 c/mL [primary endpoint], 0 vs 0.3%, respectively; Figure 2). This resulted in a treatment difference of -0.3% (95.002% CI: -1.4 to 0.8%; Mantel-Haenszel analysis adjusted for geographic region [US vs outside US]). These results were consistent with a per-protocol analysis and sensitivity analyses.

Regarding the secondary endpoint of HIV-1 RNA <50 c/mL, ISL/LEN was noninferior vs BIC/FTC/TAF per FDA Snapshot: 93.4% vs 92.4%, respectively (treatment difference, 1%; 95.002% CI: -3.2 to 5%).

Figure 2. ISLEND-1: Virologic Outcomes at Week 48[1]



In the ISL/LEN group, no participants developed resistance to either component, and rates of virologic suppression (HIV-1 RNA <50 c/mL) were similar between those with and without the M184V/I mutation at baseline: 92.3% (n/N=12/13) vs 93.7% (n/N=254/271), respectively.

Safety

Most AEs and TRAEs were Grade 1 or 2 in severity (90.8% of those with any AE and 98.8% of those with any TRAE). No deaths occurred in either group. Safety outcomes are summarized in Table 2.[1,9]

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Due to the concern regarding potential unblinding, AEs that occurred infrequently were not attributed to a treatment group. One Grade 3 treatment-related SAE of maculopapular rash occurred in a study participant (treatment group not indicated) with a history of asthma and drug allergies. One participant (treatment group not indicated) discontinued treatment after incident HBV was reported on Day 183; this participant was unvaccinated and was positive for HBsAg at Week 24 and for HBcAb at a subsequent visit. Previously elevated liver enzyme levels were noted to be normalized at the participant's Day 60 follow-up visit.[1]

Table 2. ISLEND-1: Safety Outcomes Through Week 48[1,9]

Participants, n (%)		ISL/LEN (n=304)	BIC/FTC/TAF (n=303)	Unattributed Events[a]
Any-grade AEs		241 (79.3)	238 (78.5)	–
Most common AEs (>5% in ISL/LEN group)	Upper respiratory tract infection	11.8	9.2	–
	Nasopharyngitis	7.6	4.6	–
	Diarrhea	7.2	6.3	–
	Headache	6.6	7.6	–
	Nausea	6.3	5	–
TRAEs		41 (13.5)	40 (13.2)	–
Most common TRAEs (≥2%)	Headache	3	2.6	–
	Nausea	3	3.3	–
Grade ≥3 AEs[b]		22 (7.2)	22 (7.3)	–
Treatment-related Grade ≥3 AEs		–	–	1 (0.3)
SAEs		16 (5.3)	14 (4.6)	–
Treatment-related SAEs		–	–	1 (0.3)[c]
AEs that led to discontinuation of study treatment[d]		6 (2)	5 (1.7)	–
Treatment-related AEs that led to discontinuation of study treatment		–	–	4 (1.3)
Grade 3/4 laboratory abnormalities		52 (17.2)	72 (23.8)	–
Grade 3 laboratory abnormalities		46 (15.2)	68 (22.5)	–
Grade 4 laboratory abnormalities		6 (2)	4 (1.3)	–
Most common Grade 3/4 laboratory abnormalities	Increased direct bilirubin	22 (7.3)	19 (6.3)	–
	Decreased CrCl	12 (4)	34 (11.3)	–
	Glycosuria	9 (3)	9 (3)	

[a]Due to the potential for unblinding with AEs that occurred at a low frequency, no AEs were attributed to the treatment groups.
[b]No Grade 3 AEs were reported in >1 participant; those that occurred in 1 participant (<1%) included abdominal pain, asthma, and syncope.
[c]Grade 3 treatment-related SAE of maculopapular rash.
[d]The only AE that occurred in >1 participant and resulted in treatment discontinuation was arthralgia (n=2; 0.7% overall; considered treatment-related by the investigator); their treatment group was not reported.

The mean change from baseline to Week 48 in CD4 count was -10 cells/mcL in the ISL/LEN group and -18 cells/mcL in the BIC/FTC/TAF group (LSM difference [95% CI], 12 [-16 to 39] cells/mcL). No participants in either group discontinued treatment due to a decrease in CD4 count.[1]

The mean ± SD change from baseline to Week 48 in lymphocyte count was 0.08±0.416 $\times 10^3$ cells/mcL in the ISL/LEN group and 0.08±0.493 $\times 10^3$ cells/mcL in the BIC/FTC/TAF group. No participants discontinued study treatment due to decreases in lymphocyte counts.[1]

The mean ± SD change and percent change in body weight from baseline to Week 48 was numerically similar between treatment groups overall: ISL/LEN, -0.8±5.28 kg; BIC/FTC/TAF, +0.1±5.65 kg. These results were similar when stratified by sex.[1,10]

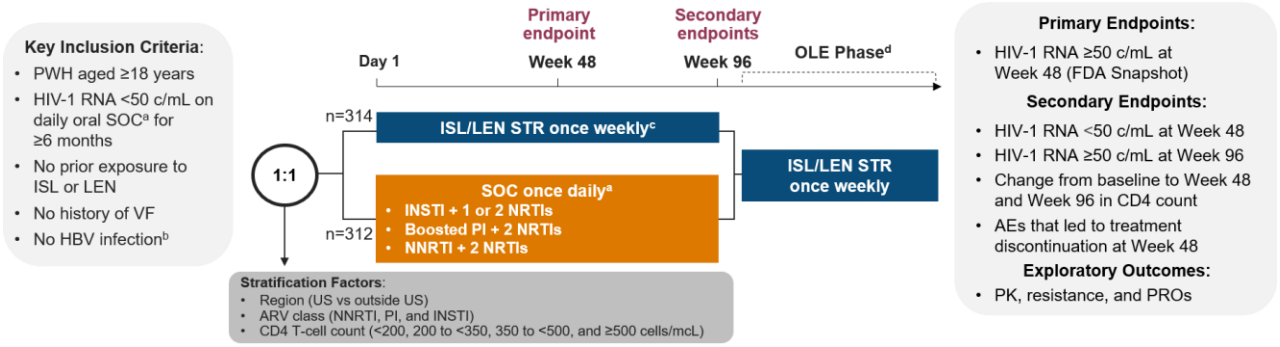
Mean ± SD adherence rates, as assessed by pill counts, were 98.9±6.71% and 95.8±9.74% in the ISL/LEN and BIC/FTC/TAF groups, respectively. Adherence rates ≥95% were achieved by numerically more participants in the ISL/LEN group than in the BIC/FTC/TAF group: 96% vs 80.4%, respectively.[1,9]

ISLEND-2 Study

Study design and demographics[2]

ISLEND-2 (NCT06630299) is an ongoing, phase 3, randomized, open-label, active-controlled, noninferiority study evaluating efficacy and safety outcomes of VS PWH receiving an SOC ARV regimen who switched to once-weekly oral ISL/LEN or remained on a daily SOC ARV regimen (Figure 3). The primary endpoint is the proportion of participants with HIV-1 RNA ≥50 c/mL at Week 48 per FDA Snapshot algorithm (noninferiority margin, 4%).

Figure 3. ISLEND-2: Study Design[2,11]



[a]SOC was administered once daily as fixed-dose combinations or STRs, except for raltegravir (dosed once or twice daily).
[b]HBsAg positive or HBcAb/HBsAb negative.
[c]Loading dose: 2 tablets of ISL/LEN (each containing 0.5 mg ISL and 300 mg LEN) on Days 1 and 2. Maintenance dose: 1 tablet (containing 2 mg ISL and 300 LEN) once weekly starting on Day 8. ISL/LEN was administered with or without food.
[d]Open-label ISL/LEN to continue until it becomes commercially available or the study is discontinued, whichever comes first.

Baseline demographics and disease characteristics are presented in Table 3.

Table 3. ISLEND-2: Baseline Demographics and Disease Characteristics[2]

Key Demographics and Characteristics		Total (N=626)	ISL/LEN (n=314)	SOC (n=312)
Age, median (IQR), years		52 (42–60)	52 (42–60)	53 (43–61)
Age ≥50/≥65 years, n (%)		364 (58)/89 (14)	180 (57)/47 (15)	184 (59)/42 (13)
Assigned female sex at birth, n (%)		211 (34)	105 (33)	106 (34)
Race,[a] n (%)	White	264 (42)	130 (41)	134 (43)
	Black	193 (31)	94 (30)	99 (32)
	Asian	119 (19)	61 (19)	58 (19)
	Other[b]	27 (4)	17 (5)	10 (3)
Ethnicity,[a] Hispanic or Latinx, n (%)		123 (20)	62 (20)	61 (20)
Geographical region, n (%)	US	324 (52)	162 (52)	162 (52)
	Outside of US	302 (48)	152 (48)	302 (48)
CD4, mean ± SD, cells/mcL		778±333.2	795±346.4	761±319
<200 cells/mcL, n (%)		8 (1)	3 (1)	5 (2)
Lymphocytes, mean ± SD, × 10^3 cells/mcL		1.96±0.624	1.99±0.631	1.94±0.616

Key Demographics and Characteristics		Total (N=626)	ISL/LEN (n=314)	SOC (n=312)
Number of ARV pills/day, n (%)	1 pill	552 (88)	277 (88)	275 (88)
	2 pills	53 (8)	24 (8)	29 (9)
	3 pills	20 (3)	12 (4)	8 (3)
ARV class, n (%)	INSTI + 1 or 2 NRTIs	478 (76)	245 (78)	233 (75)
	DTG/3TC	189 (30)	88 (28)	101 (32)
	BIC/FTC/TAF	72 (12)	34 (11)	38 (12)
	NNRTI + 2 NRTIs	95 (15)	43 (14)	52 (17)
	PI + 2 NRTIs	53 (8)	26 (8)	27 (9)

Abbreviations: 3TC=lamivudine; DTG=dolutegravir.
[a]Local regulations prohibited data collection of race (ISL/LEN, n=12 [4%]; SOC, n=11 [4%]) and ethnicity (ISL/LEN, n=16 [5%]; SOC, n=12 [4%]).
[b]Included American Indian or Alaska Native or other.

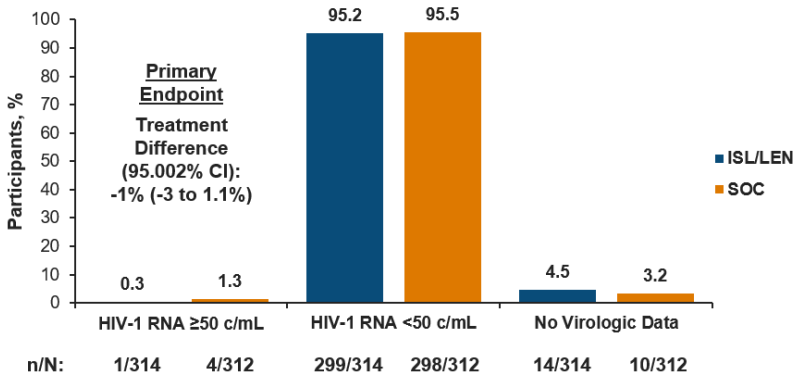
Week 48 results

Efficacy[2]

At Week 48, ISL/LEN demonstrated noninferior efficacy (HIV-1 RNA ≥50 c/mL; primary endpoint) compared with staying on SOC (0.3% vs 1.3%, respectively; Figure 4). This resulted in a treatment difference of -1% (95.002% CI: -3 to 1.1%; Mantel-Haenszel analysis adjusted for geographic region [US vs outside US] and ARV class [INSTI, NNRTI, and PI]). ISL/LEN was deemed non-inferior to SOC but not superior to SOC, with the upper bound of the 95.002% CI <4% and >0%.

For the secondary endpoint of HIV-1 RNA <50 c/mL, similar rates of suppression were noted: ISL/LEN, 95.2%; SOC, 95.5% (Figure 4). In the ISL/LEN group, no participants developed resistance to either component; the participant with HIV-1 RNA ≥50 c/mL had low-level viremia (104 c/mL at Week 48), did not meet the criteria for resistance testing, and was resuppressed on ISL/LEN at Week 60. Three of the 4 participants in the SOC group with HIV-1 RNA ≥50 c/mL did not meet criteria for resistance testing and were later resuppressed. The fourth participant had HIV-1 RNA of 621 c/mL at Week 48 and was resuppressed at Week 60, and their resistance testing was conducted twice (both resulted in assay failure).

Figure 4. ISLEND-2: Virologic Outcomes at Week 48[2]



Safety

The median (IQR) exposure to ISL/LEN was 60 (56.1–66.4) weeks and 59.3 (55.6–65.2) weeks for SOC. Treatment with ISL/LEN was well tolerated, and no Grade ≥3 TRAEs occurred in either group. All TRAEs were Grade 1 or 2 in severity

One treatment-related SAE of seizure occurred in a participant who missed 2 doses of antiseizure medication in the ISL/LEN group (no interruptions of ISL/LEN doses); none occurred in the SOC group.[2]

Table 4. ISLEND-2: Safety Outcomes Through Week 48[2,11]

Participants, n (%)		ISL/LEN (n=314)	SOC (n=312)
Any treatment-emergent AEs		249 (79)	241 (77)
Most common treatment-emergent AEs (>5% in ISL/LEN group)	Upper respiratory tract infection	37 (11.8)	27 (8.7)
	Headache	30 (9.6)	5 (1.6)
	Nasopharyngitis	25 (8)	20 (6.4)
	Arthralgia	25 (8)	15 (4.8)
	Diarrhea	16 (5.1)	9 (2.9)
	Dizziness	16 (5.1)	5 (1.6)
TRAEs		58 (18)	1 (<1)
Most common TRAEs (≥2% in ISL/LEN group)	Headache	15 (4.8)	0
	Diarrhea	10 (3.2)	0
	Nausea	9 (2.9)	0
Grade ≥3 AEs[a]		24 (8)	28 (9)
SAEs		22 (7)	27 (9)
Treatment-related SAEs		1 (<1)[b]	0
AEs that led to study drug discontinuations		2 (1)[c]	1 (<1)[d]
Deaths		1 (<1)[e]	2 (1)[f]
Grade 3/4 laboratory abnormalities		66 (21)	81 (26)
Most common Grade 3/4 laboratory abnormalities	Increased direct bilirubin concentrations	28 (9)	17 (5)
	Glycosuria	13 (4)	13 (4)
	Decreased CrCl	9 (3)	36 (12)

[a]Only two Grade ≥3 treatment-emergent AEs occurred in >1 participant: acute kidney injury (ISL/LEN, n=2 [0.6%]); SOC, n=3 [1%]) and road traffic accident (ISL/LEN, n=2 [0.6%]; SOC, n=0).
[b]Grade 2 seizure in a participant who missed 2 doses of antiseizure medication, n=1.
[c]Treatment-related hyperbilirubinemia in a participant with a history of hyperbilirubinemia, n=1; acute HBV unrelated to treatment in a participant with no priori immunity to HBV, n=1.
[d]Central nervous system lymphoma unrelated to treatment, n=1.
[e]Road traffic accident, n=1; unrelated to study drug.
[f]Pneumonia, which was complicated by cardiogenic shock/cardiac arrest, n=1; central nervous system lymphoma, n=1. None were deemed to be related to study drug.

Among the participants who had a Grade ≥3 increase in direct bilirubin, most increases were not clinically significant, with median (IQR) changes from baseline of +0.1 (-0.2 to 0.05) mg/dL in the ISL/LEN group and -0.01 (-0.04 to 0.02) mg/dL in the SOC group. Among those with clinically significant increases, most participants had underlying health conditions or concomitant medications that were identified as causes of the increases.
Three participants in the ISL/LEN group with elevated direct bilirubin levels also had elevations in other liver parameters (n=1 each: acute syphilis treated with penicillin, acute HBV infection, and gastroenteritis), and all had normalized or improved values at the next study visits.[2]

The mean percent (95% CI) change from baseline to Week 48 in CD4 count was -0.2% (-4.2% to 3.9%) in the ISL/LEN group and +2.4% (-0.8% to 5.6%) in the SOC group (LSM difference [95% CI], -2% [-6.8% to 2.8%]). No participants in either group discontinued treatment due to a decrease in CD4 count.[2]

In a post hoc analysis using the mean CD4 count at baseline and Day 1, the mean ± SD change from baseline to Week 48 was -43±165 cells/mcL in the ISL/LEN group and -17±160.6 cells/mcL in the SOC group (treatment difference [95% CI]: -23 [-47 to 2] cells/mcL).[2]

In an analysis of changes in CD4 count categories (<200, 200 to <350, 350 to <500, and ≥500 cells/mcL) from baseline and Week 48 in participants with available data (ISL/LEN, n=301; SOC, n=302), 21 participants (7%) moved to a lower category and 26 (9%) moved to a higher category in the ISL/LEN group, whereas 20 participants (7%) moved to a lower category and 24 (8%) moved to a higher category in the SOC group.[2]

Mean ± SD changes from baseline through Week 48 in lymphocyte counts were generally stable in each group: ISL/LEN, -0.02±0.442× 10^3 cells/mcL; SOC, 0.1±0.447 × 10^3 cells/mcL. No participants discontinued study treatment due to decreases in lymphocyte counts.[2]

Through Week 48, mean ± SD changes in body weight in each group were minimal: ISL/LEN, +0.1±4.74 kg; SOC, -0.3±4.12 kg.[2]

Two pregnancies occurred during the study. In the ISL/LEN group, 1 participant who had preexisting Type 2 diabetes mellitus became pregnant and was admitted to the hospital due to poor glycemic control; they delivered an infant with reassuring Apgar scores at gestation Week 33. A participant in the SOC group became pregnant, stayed in the study, and later had a spontaneous abortion (considered a Grade ≥3 AE and an SAE; not considered to be treatment-related).[2,11]

Adherence[2,11]

Adherence rates were calculated as follows: (total number of tablets administered/tablets expected to be administered on treatment) × 100. For assessments of adherence level, the denominator for calculations was the number of participants who were on treatment, returned ≥1 study bottle, and had calculable adherence data. The median adherence rate was 100% in the ISL/LEN group, and most participants (98%; n/N=307/312) took ≥90% of the ISL/LEN doses. Of the 5 participants with an adherence rate <90% (3 had a rate <80%), 4 had an HIV-1 RNA <50 c/mL at Week 48, and 1 discontinued participation in the study while VS due to a protocol violation.

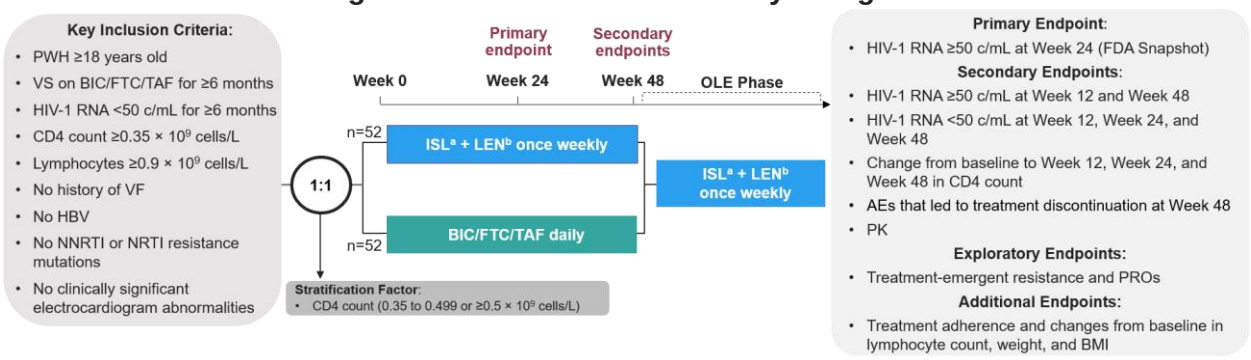
Phase 2 Clinical Studies on the Use of LEN and ISL

Study GS-US-563-6041

Study design and demographics[3]

Study GS-US-563-6041 (NCT05052996) is an ongoing, phase 2, open-label, active-controlled clinical trial comparing efficacy and safety in VS PWH treated with BIC/FTC/TAF who switched to weekly doses of oral ISL 2 mg + LEN 300 mg or remained on once-daily BIC/FTC/TAF (Figure 5). The primary endpoint is the proportion of participants with HIV-1 RNA ≥50 c/mL at Week 24 per the FDA Snapshot algorithm. The study was not powered for analysis.

Figure 5. GS-US-563-6041: Study Design[3,12]



[a]Dose: 2 mg (2 × 1 mg capsule) ISL on Day 1 and every week thereafter starting on Day 8.
[b]Loading dose: 600 mg (2 × 300 mg tablets) LEN on Day 1 and Day 2. Maintenance dose: 300 mg (1 × 300 mg tablet) on Day 8 and every week thereafter.

Baseline demographics and disease characteristics are presented below (Table 5).

Table 5. GS-US-563-6041: Baseline Demographic and Disease Characteristics[3]

Key Demographics and Characteristics		Total (N=104)	ISL + LEN (n=52)	BIC/FTC/TAF (n=52)
Age, mean (range), years		44 (26–76)	43 (28–67)	45 (26–76)
Assigned female sex at birth, n (%)		19 (18.3)	10 (19.2)	9 (17.3)
Race,[a] 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 (1.1)	0	1 (1.9)
	Other	8 (7.7)	3 (5.8)	5 (9.6)
Ethnicity, Hispanic or Latinx, n (%)		30 (28.8)	13 (25)	17 (32.7)
CD4, mean ± SD, × 10^9 cells/L		0.786±0.2495	0.755±0.2236	0.818±0.2713
Lymphocytes, mean ± SD, × 10^3/mcL		1.94±0.556	1.94±0.445	1.95±0.652
Weight, median (IQR), kg		80.5 (74.4–88.7)	80.5 (74.4–88.7)	83.2 (76.1–92.5)
BMI, median (IQR), kg/m^2		27.1 (24.5–29.4)	26.9 (23.8–30)	27.2 (25.5–29.3)

Week 24 and 48 results

Efficacy[3]

At Week 24, 1 participant (1.9%) in the ISL + LEN group and none in the BIC/FTC/TAF group had HIV-1 RNA ≥50 c/mL (primary endpoint); this resulted in a treatment difference of 1.9% (95% CI: -5.2 to 10.5%). The ISL + LEN participant had HIV-1 RNA levels of 251 c/mL on Day 1 and <200 c/mL at Week 24 and was suppressed after Week 36 and maintained virologic suppression through Week 48 on ISL + LEN. This participant did not develop resistance to either component by genotypic or phenotypic analysis. In both groups, 94.2% of participants achieved HIV-1 RNA <50 c/mL at Week 24; data were missing for 2 participants (3.8%) in the ISL + LEN group and 3 (5.8%) in the BIC/FTC/TAF group.

At Week 48, 94.2% of participants were VS in the ISL + LEN group and 92.3% were in the BIC/FTC/FTC group (treatment difference: 1.9%; 95% CI: -9.3 to 13.6%). No participants in the either group had HIV-1 RNA ≥50 c/mL; data were missing for 3 participants (5.8%) in the ISL + LEN group and 4 (7.7%) in the BIC/FTC/TAF group. None of the participants with missing data at Week 24 or 48 had virologic rebound (HIV-1 RNA ≥50 c/mL) at their last visit with available data.

At Week 48, 3 participants discontinued ISL + LEN (AEs unrelated to study drug, n=2; other reasons, n=1), and 4 discontinued BIC/FTC/TAF (reasons not related to study drug, n=3; missing data but remained on study drug, n=1). All participants had HIV-1 RNA <50 c/mL at study discontinuation.

Safety and adherence[3]

At Week 48, no Grade ≥3 AEs, SAEs, or AEs leading to study drug discontinuation were related to study drug. All TRAEs were Grade 1 or 2 in severity (ISL + LEN, 19.2%; BIC/FTC/TAF, 5.8%); the only TRAEs that occurred in ≥2 participants in the ISL + LEN group were dry mouth and nausea (each, 3.8%). No Grade 3 and 4 laboratory abnormalities were clinically significant, except for alanine aminotransferase elevation in a participant in the ISL + LEN group with acute HBV infection.

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.

The median (IQR) adherence rate was 100% (98.8–100%) in the ISL + LEN group and 98.8% (97.1–100%) in the BIC/FTC/TAF group. A higher proportion of participants in the ISL + LEN group than in the BIC/FTC/TAF group had an adherence rate of ≥95%: 98% vs 86.3%, respectively.

Week 96 results

Efficacy

All enrolled participants had the option to continue into a 48-week extension phase to receive ISL + LEN. The early switch group consisted of the 52 participants initially randomized to receive ISL + LEN and continued on it in the OLE, and the late switch group consisted of the 45 participants who were initially randomly assigned to receive BIC/FTC/TAF and switched to ISL + LEN in the OLE.[4,5] Baseline characteristics were similar between the two OLE groups; overall, the median age was 40 years, 18.6% were assigned female at birth, and 50.5% were White.[5]

At Week 96, all participants in both treatment groups with virologic data available had HIV-1 RNA ≤50 c/mL (early switch group, 88.5% [n/N=46/52]; late switch group, 97.8% [n/N=44/45]). Data were unavailable for 11.5% of participants (n/N=6/52) in the early switch and 2.2% (n/N=1/45) in the late switch group.[4,5]

Safety and adherence[4,5]

No Grade ≥3 TRAEs, SAEs, or AEs related to ISL + LEN that led to study drug discontinuation were reported (Table 6).

Table 6. GS-US-563-6041: Safety Outcomes With ISL + LEN Through Week 96[4,5]

Participants, n (%)		Total (N=97)	Early Switch Group (n=52)	Late Switch Group (n=45)
Any AEs		81 (83.5)	46 (88.5)	35 (77.8)
TRAEs		12 (12.4)	10 (19.2)	2 (4.4)
Most common TRAEs (≥2 participants in any group	Dry mouth	2 (2.1)	2 (3.8)	0
	Nausea	2 (2.1)	2 (3.8)	0
	Fatigue	2 (2.1)	1 (1.9)	1 (2.2)

Participants, n (%)	Total (N=97)	Early Switch Group (n=52)	Late Switch Group (n=45)
SAEs	3 (3.1)[a]	3 (5.8)	0
AEs that led to study drug discontinuation	2 (2.1)[b]	2 (3.8)	0

[a]Neurologic anesthesia complication (n=1), renal colic/colon perforation in the same participant (n=1); pneumonia (n=1).
[b]Acute HBV infection (n=1) and renal colic/colon perforation (n=1) in the same participant. These were not considered TRAEs.

There were no clinically significant changes in CD4 or lymphocyte counts from baseline through Week 96 in both groups. Body weight and body mass index remained stable from baseline through Week 96 in both groups.

Mean adherence to weekly oral ISL + LEN, as calculated by pill count, remained high in the early switch (99.3%) and late switch (98.6%) treatment groups. No VF was observed, and no emergent resistance to ISL or LEN was detected.

Terms of Collaboration[13]

Under the terms of the agreement, Gilead and Merck will co-develop and co-commercialize long-acting products to treat PWH that combine Gilead's LEN and Merck's proprietary investigational nucleoside reverse transcriptase translocation inhibitor, ISL. 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.

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Abbreviations

AE=adverse event
ARV=antiretroviral
BIC=bictegravir
c/mL=copies per mL
CD4=cluster of differentiation 4
FTC=emtricitabine
HBcAb=hepatitis B core antibody
HBsAb=hepatitis B surface antibody
HBsAg=hepatitis B surface antigen
INSTI=integrase strand transfer inhibitor
ISL=islatravir
LEN=lenacapavir
LSM=least-squares mean
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OLE=open-label extension
PI=protease inhibitor
PK=pharmacokinetic(s)
PRO=participant-reported outcome
PWH=people with HIV-1
SAE=serious adverse event
SOC=standard of care
STR=single-tablet regimen
TAF=tenofovir alafenamide
TRAE=treatment-related adverse event
VF=virologic failure
VS=virologically suppressed

Follow Up

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

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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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