Once-Weekly Oral Islatravir/Lenacapavir (ISL/LEN) Versus Daily Standard-of-Care (SOC) Therapy in Virologically Suppressed Adults With HIV-1: Week 48 Results of the ISLEND-2 Phase 3 Trial

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Disclosures

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- **Princy N Kumar** participated on data safety monitoring boards or advisory boards for Gilead Sciences, Inc., GSK, Merck, and ViiV Healthcare, received grants or contracts (paid to their institution) from Gilead Sciences, Inc., GSK, Merck, Theratechnologies, and ViiV Healthcare; payments (paid to their institution) for industry-sponsored clinical trials from Merck; and holds stock or stock options in Gilead Sciences, Inc., GSK, Johnson & Johnson, Merck, Moderna, Pfizer, Theratechnologies, and ViiV Healthcare. **Peter J Ruane** received honoraria for speaker's bureaus from Gilead Sciences, Inc. and ViiV Healthcare. **Ploenchan Chetchotisakd** and **Winai Ratanasuwan** have no conflicts of interest to report. **Afaaf Liberty** received payments (paid to their institution) for industry-sponsored clinical trials from GSK and MSD. **Ronald G Nahass** received grants or contracts from GSK, Merck, and ViiV Healthcare; and is President of the Infectious Diseases Society of America. **Alejandro Arenas-Pinto** received payment for advisory board participation from ViiV Healthcare. **Frank A Post** received support for attending meetings and/or travel from Gilead Sciences, Inc. and MSD; and grants or contracts (paid to their institution) from Gilead Sciences, Inc., Immunocore, MSD, and ViiV Healthcare. **David A Baker** received grants and honoraria for presentations from ViiV Healthcare. **Pedro Cahn** received grants or contracts from ViiV Healthcare; consulting fees from Gilead Sciences, Inc., Merck, and ViiV Healthcare; and honoraria for presentations from ViiV Healthcare. **Eveline Hofmann** received payment (paid to their institution) for attending meetings and/or travel from AstraZeneca and Gilead Sciences, Inc. **Dai Watanabe** received grants for clinical trials (paid to their institution) from AbbVie GK, CMIC, Gilead Sciences K.K., GSK K.K., MSD K.K., and ViiV Healthcare K.K.; and honoraria for presentations from Gilead Sciences K.K., MSD K.K., Shionogi, and ViiV Healthcare K.K. **Po-Liang Lu** received honoraria for presentations and support for attending meetings from Gilead Sciences, Inc. **Anna H E Roukens** received grants or contracts for industry-sponsored clinical trials from Gilead Sciences, Inc. **Miłosz Parczewski** received grants or contracts (paid to their institution) from the Agency for Medical Research, Poland, and National Science Centre, Poland; honoraria for presentations (paid to their institution) from AbbVie, Gilead Sciences, Inc., GSK, Janssen, MSD, Pfizer, and ViiV Healthcare; participated in advisory boards for Gilead Sciences, Inc., GSK, MSD, and ViiV Healthcare; and holds an unpaid position as President of the European AIDS Clinical Society. **Devi SenGupta** is an employee and shareholder of Gilead Sciences, Inc.; is co-chair of the IAS HIV Cure Industry Collaborative Group, board member of the San Francisco AIDS Foundation, and advisory council member of the California HIV Research Program. **Hongyuan Wang**, **Fadi Shihadeh**, **Hadas Dvory-Sobol**, and **Martin S Rhee** are employees and shareholders of Gilead Sciences, Inc. **Ke Chen**, **Melissa Shaughnessy**, and **Cyril Llamoso** are employees and shareholders of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. (Rahway, NJ, USA). **Onyema Ogbuagu** received consulting fees from Gilead Sciences, Inc., Merck, and ViiV Healthcare; honoraria for presentations and support to attend meetings and/or travel from Gilead Sciences, Inc.

Summary Slide

What is your main question?

- To assess the efficacy, safety, and tolerability of a novel investigational once-weekly single-tablet treatment regimen of islatravir/lenacapavir (ISL/LEN) compared with daily oral SOC treatment for HIV-1

What did you find?

- In people with HIV-1 who were virologically suppressed on SOC daily oral therapy, switching to once-weekly oral ISL/LEN was well tolerated and maintained a high rate of virologic suppression, with efficacy noninferior to that of daily SOC at Week 48. No treatment-emergent resistance to ISL/LEN was identified to date

Why is it important?

- New treatment options, including oral treatments with longer dosing intervals, are needed to meet the diverse circumstances and preferences of people with HIV-1, and could help reduce some of the barriers to sustained virologic suppression

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ISL, islatravir; **LEN**, lenacapavir; **SOC**, standard-of-care.

Background and Objectives

- PWH on daily oral treatment have expressed strong interest in long-acting oral options,[1,2] which could help meet their diverse treatment needs and improve outcomes[1-4]
- The combination of islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor,[5,6] and lenacapavir (LEN), a capsid inhibitor,[7] is being developed as a once-weekly oral single-tablet regimen for virologically suppressed PWH
- ISL and LEN have distinct mechanisms of action, potent anti–HIV-1 activity, nonoverlapping resistance profiles, and are well suited for development as a long-acting oral combination therapy due to their long half-lives that allow for weekly dosing[8-10]
- In a Phase 2 study in virologically suppressed PWH, once-weekly oral ISL + LEN was well tolerated, and maintained high efficacy through Week 96[11,12]

We present Week 48 analyses of the ISLEND-2 study evaluating the switch to once-weekly oral ISL/LEN from daily SOC in virologically suppressed PWH

1. Derrick CB, et al. *Open Forum Infect Dis.* 2018;5(10):ofy247. 2. Graham SM, et al. *J Int AIDS Soc.* 2023;26 Suppl 2(Suppl 2):e26099. 3. Stout JA, et al. *AIDS Behav.* 2024;28(10):3315-25. 4. Nachega JB, et al. *Lancet HIV.* 2023;10(5):e332-42. 5. Michailidis E, et al. *J Biol Chem.* 2014;289(35):24533-48. 6. Salie ZL, et al. *Proc Natl Acad Sci USA.* 2016;113(33):9274-9. 7. Link JO, et al. *Nature.* 2020;584(7822):614-8. 8. Segal-Maurer S, et al. *N Engl J Med.* 2022;386(19):1793-803. 9. Matthews RP, et al. *Clin Transl Sci.* 2021;14(5):1935-44. 10. Diamond TL, et al. *Antimicrob Agents Chemother.* 2024;68(7):e0033424. 11. Colson AE, et al. *Ann Intern Med.* 2026;179(2):168-76. 12. Colson AE, et al. *Top Antivir Med.* 2026;34(1):583 [Abstract 516].
ISL, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1; **SOC**, standard-of-care.

ISL/LEN Phase 3 Development Program

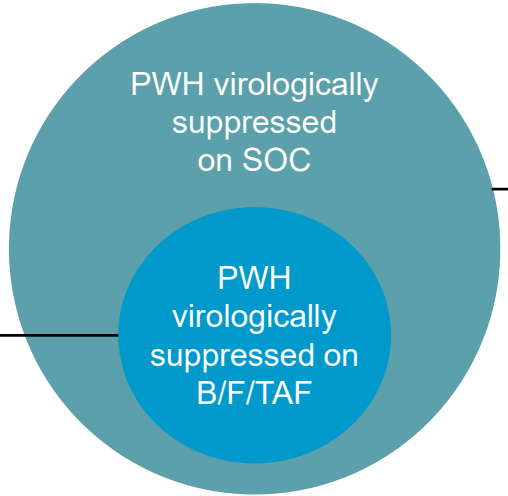
PWH With Virologic Suppression

ISLEND-1

Phase 3, **double-blind**, registrational trial evaluating the efficacy and safety of once-weekly oral ISL/LEN STR compared with daily oral B/F/TAF[1]

Week 48 results from ISLEND-1 will be presented later today:

"ARTistic strategies 2: The long game"
15:00–16:00 (OAB1406LB)
Session room: 202



ISLEND-2

Phase 3, **open-label**, registrational trial evaluating the efficacy and safety of once-weekly oral ISL/LEN STR compared with daily oral SOC[2]

Results presented here

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1; **SOC**, standard-of-care; **STR**, single-tablet regimen.
1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06630286 (accessed June 30, 2026). 2. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06630299 (accessed June 30, 2026).

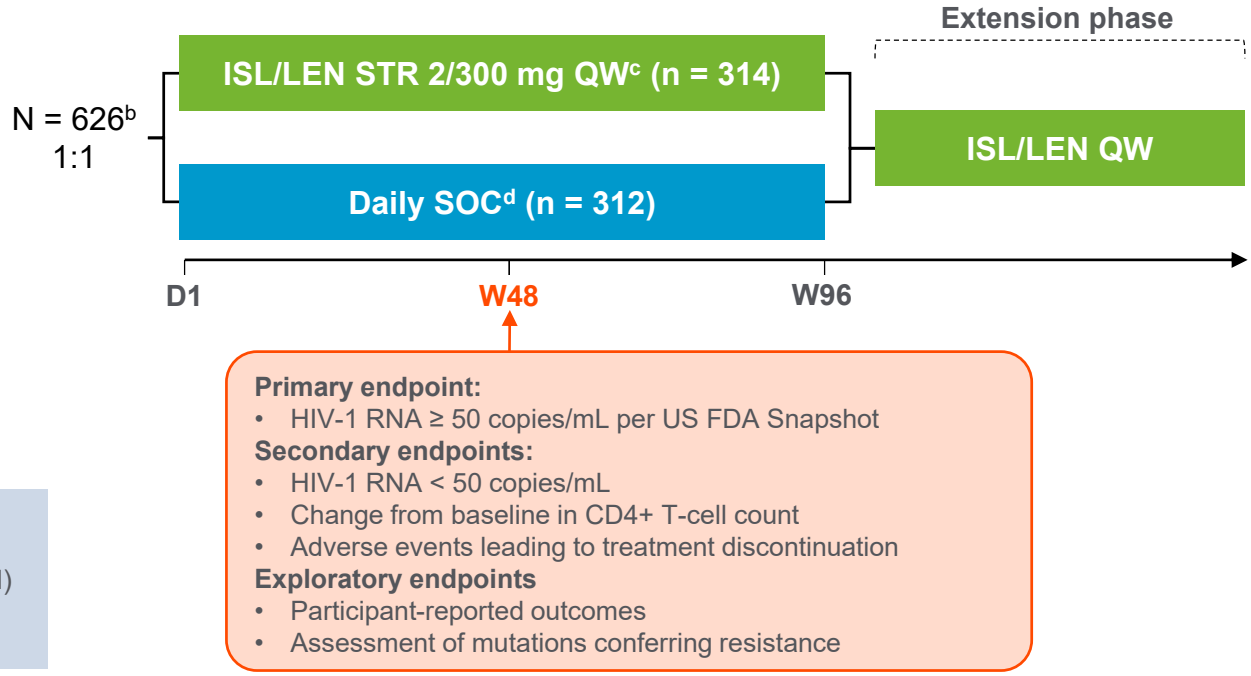
Study Design: Global Trial at 100 Sites[1]

ISLEND-2: Phase 3, open-label, active-controlled noninferiority study in virologically suppressed PWH

Eligibility criteria:
- Age ≥ 18 years
- HIV-1 RNA < 50 copies/mL for ≥ 6 months on daily oral SOC
- No prior exposure to ISL or LEN
- No history of virologic failure
- No HBV infection[a]

SOC:
- INSTI + 1 or 2 NRTIs
- bPI + 2 NRTIs
- NNRTI + 2 NRTIs

Stratification:
- Region (US vs non-US)
- Antiretroviral class (NNRTI, PI, and INSTI)
- CD4+ T-cell count (< 200, 200 to < 350, 350 to < 500, and ≥ 500 cells/μL)



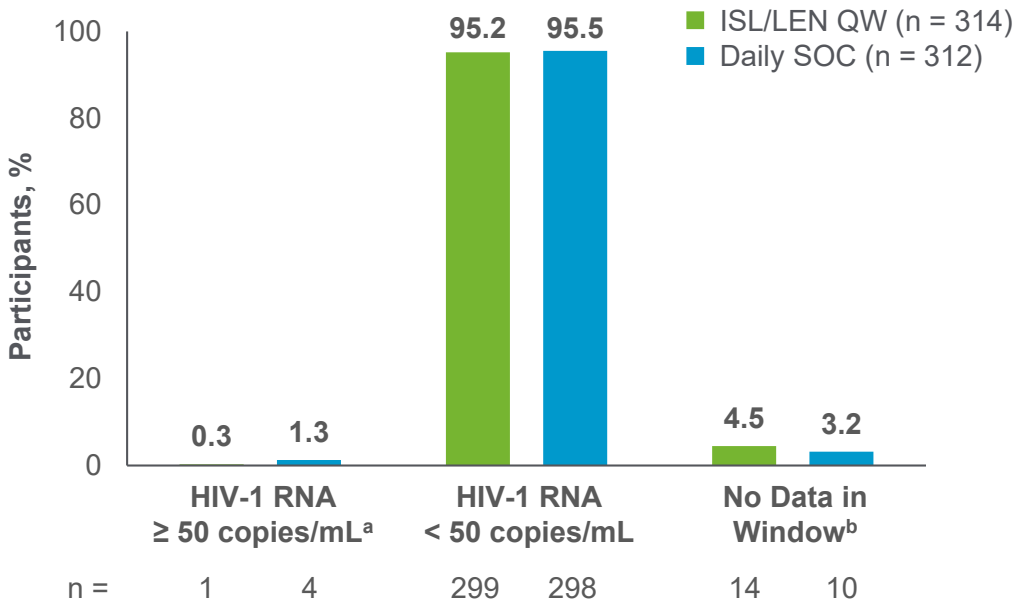
[a]Defined as surface antigen positive or core antibody positive/surface antibody negative. [b]Randomized: N=634, dosed: N=626. [c]Initiation/loading dose of ISL/LEN 0.5/300 mg × 2 tablets on Days 1 and 2, then an ISL/LEN STR 2/300 mg tablet once weekly from Day 8, without regard to food. [d]All SOC treatments were taken once daily, including FDC and STRs, except for raltegravir, which could be taken once or twice daily. **b**, boosted; **D**, Day; **FDC**, fixed-dose combination; **HBV**, hepatitis B virus; **INSTI**, integrase strand-transfer inhibitor; **ISL**, islatravir; **LEN**, lenacapavir; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **NRTI**, nucleoside/nucleotide reverse transcriptase inhibitor; **PI**, protease inhibitor; **PWH**, people with HIV-1; **QW**, once weekly; **SOC**, standard-of-care; **STR**, single-tablet regimen; **W**, Week. 1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06630299 (accessed April 16, 2026).

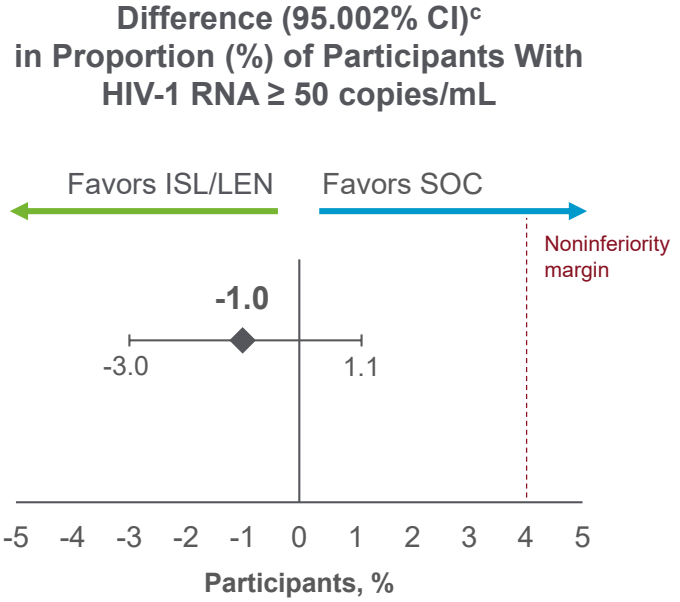
Baseline Demographic and Clinical Characteristics

	ISL/LEN QW (n = 314)	Daily SOC (n = 312)	Total (N = 626)
Age, years, median (IQR)	52 (42–60)	53 (43–61)	52 (42–60)
Age ≥ 65 years, n (%)	47 (15)	42 (13)	89 (14)
Assigned female at birth, n (%)	105 (33)	106 (34)	211 (34)
Race, n (%)[a]			
White	130 (41)	134 (43)	264 (42)
Black	94 (30)	99 (32)	193 (31)
Asian	61 (19)	58 (19)	119 (19)
Other[b]	17 (5)	10 (3)	27 (4)
Ethnicity: Hispanic or Latine, n (%)[a]	62 (20)	61 (20)	123 (20)
Antiretroviral medication class, n (%)			
INSTI	245 (78)	233 (75)	478 (76)
NNRTI	43 (14)	52 (17)	95 (15)
PI	26 (8)	27 (9)	53 (8)
Daily single-tablet regimen, n (%)	277 (88)	275 (88)	552 (88)
CD4+ T-cell count, cells/μL, mean (SD)	795 (346.4)	761 (319.0)	778 (333.2)
Lymphocyte count × 10^3 cells/μL, mean (SD)	1.99 (0.63)	1.94 (0.62)	1.96 (0.62)
BMI, kg/m^2, median (IQR)	27.0 (23.9, 30.7)	26.7 (23.9, 30.5)	26.9 (23.9, 30.6)

[a]Local regulators did not allow collection of race in 23 participants (ISL/LEN, n = 12 [4%]; SOC, n = 11 [4%]) or ethnicity in 28 participants (ISL/LEN, n = 16 [5%]; SOC, n = 12 [4%]).
[b]Category includes American Indian or Alaska Native, and Other.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BMI**, body mass index; **DTG/3TC**, dolutegravir/lamivudine; **INSTI**, integrase strand-transfer inhibitor; **ISL**, islatravir; **LEN**, lenacapavir; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **PI**, protease inhibitor; **QW**, once weekly; **SOC**, standard-of-care.

Virologic Outcomes (FDA Snapshot) at Week 48

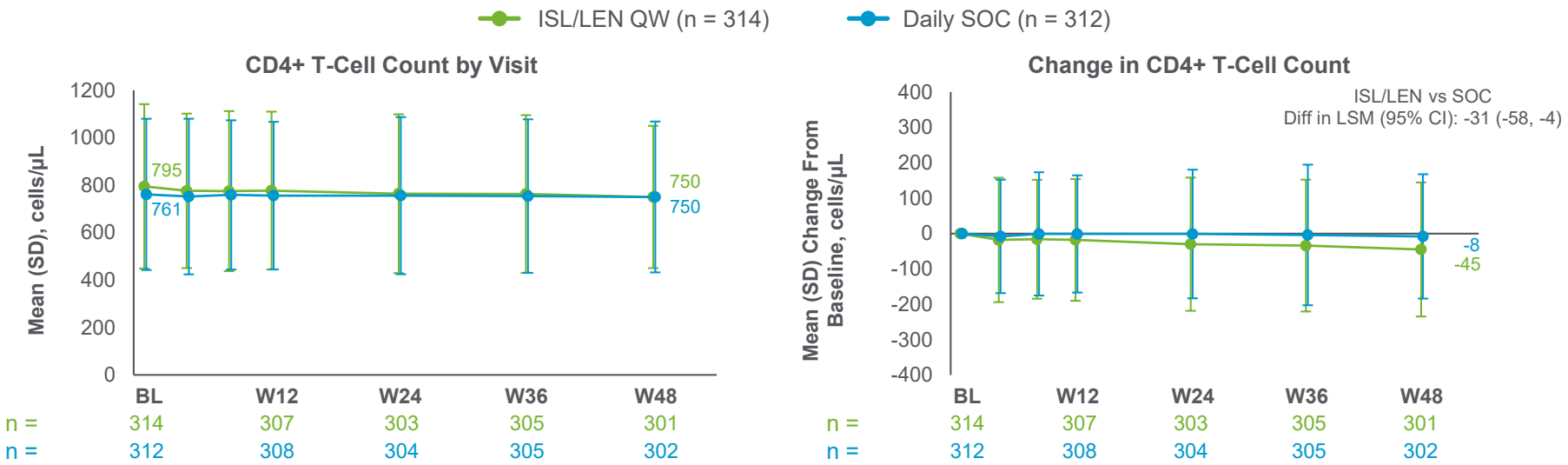




- Efficacy of once-weekly oral ISL/LEN was noninferior to that of daily SOC
- Participants in both treatment groups maintained high rates of virologic suppression
- No emergent resistance to ISL or LEN was detected through Week 48

[a]HIV-1 RNA ≥ 50 copies/mL in Week 48 window: ISL/LEN, n = 1; SOC, n = 4. [b]Discontinued study drug due to adverse event or death: ISL/LEN, n = 3; SOC, n = 2. Discontinued study drug due to other reasons and last available HIV-1 RNA was< 50 copies/mL: ISL/LEN, n = 9; SOC, n = 4. Missing data during analysis window but still on study drug: ISL/LEN, n = 2; SOC, n = 4. [c]Difference (ISL/LEN minus SOC) and two-sided 95.002% CI were constructed based on stratum-adjusted Mantel-Haenszel proportion adjusted by geographic region (US vs non-US) and antiretroviral class (NNRTI, PI, and INSTI); NI was achieved if the upper bound of the 95.002% CI was < 4%; superiority was assessed if NI was achieved and concluded if the upper bound was < 0%.
INSTI, integrase strand-transfer inhibitor; **ISL**, islatravir; **LEN**, lenacapavir; **NI**, noninferiority; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **PI**, protease inhibitor; **QW**, once weekly; **SOC**, standard-of-care.

CD4+ T-cell Count Changes Through Week 48



- Mean percentage changes (95% CI) from baseline in CD4+ T-cell count at Week 48 were similar between groups (ISL/LEN: -0.2% [-4.2, 3.9]; SOC: 2.4% [-0.8, 5.6])
- Lymphocyte counts remained stable in both treatment groups (mean change at Week 48: ISL/LEN, -0.02 × 10^3 cells/µL; SOC, 0.10 × 10^3 cells/µL)
- No participants discontinued due to decreases in CD4+ T-cell or lymphocyte counts

BL, baseline; **Diff**, difference; **ISL**, islatravir; **LEN**, lenacapavir; **LSM**, least squares mean; **QW**, once weekly; **SOC**, standard-of-care; **W**, Week.

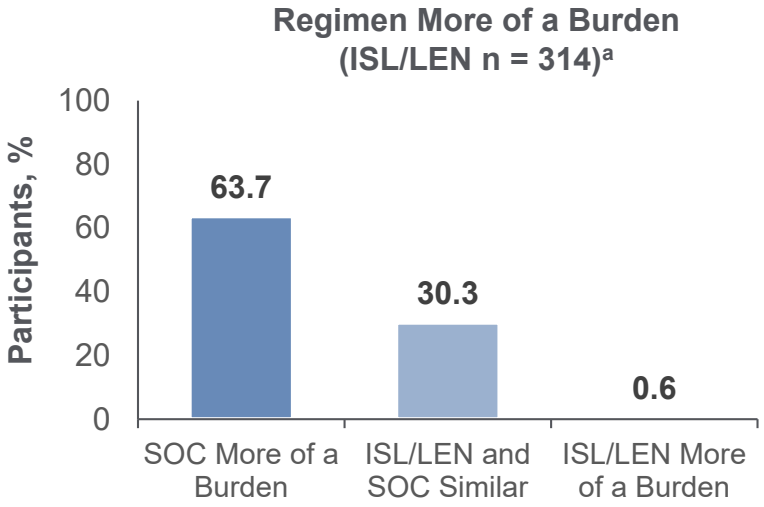
Safety Profile Overview

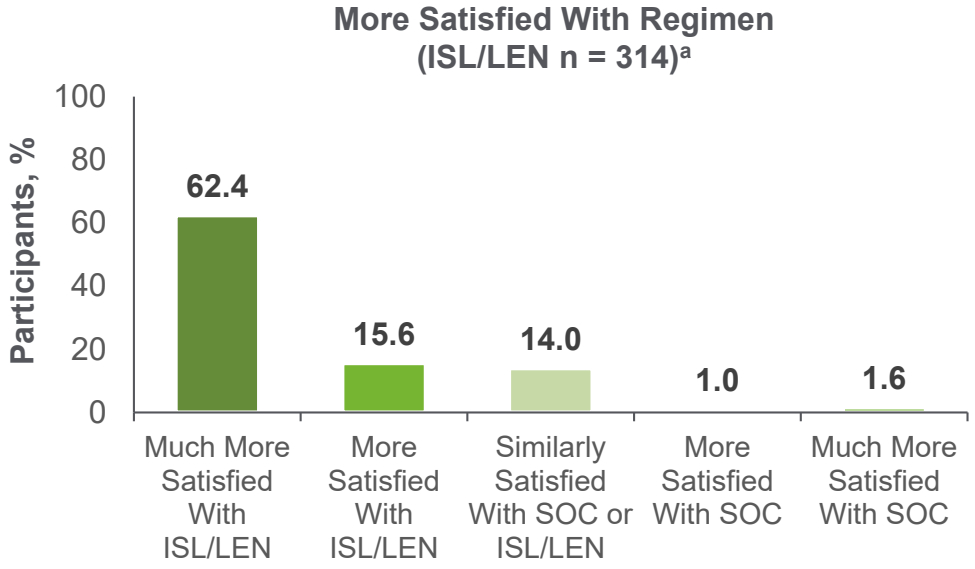
Participants, n (%)	ISL/LEN QW (n = 314)	Daily SOC (n = 312)
Any AE	249 (79)	241 (77)
Grade ≥ 3	24 (8)	28 (9)
Treatment-related AEs	58 (18)	1 (< 1)
Grade ≥ 3	0	0
Most common (≥ 2% in the ISL/LEN group)		
Headache	15 (5)	0
Diarrhea	10 (3)	0
Nausea	9 (3)	0
Serious AEs	22 (7)	27 (9)
Treatment related[a]	1 (< 1)	0
AEs leading to study drug discontinuation[b]	2 (1)	1 (< 1)
Deaths[c]	1 (< 1)	2 (1)

- Body weight remained stable throughout 48 weeks in both treatment groups, with a mean (SD) change from baseline of 0.1 (4.74) kg in the ISL/LEN group and -0.3 (4.12) kg in the SOC group

Severity grades were defined by the DAIDS Toxicity Grading Scale, version 2.1.
[a]ISL/LEN: seizure (n = 1). [b]ISL/LEN: hyperbilirubinemia in a participant with prior history of hyperbilirubinemia (n = 1, related to treatment) and acute hepatitis B (n = 1, unrelated to treatment); SOC: central nervous system lymphoma (n = 1, unrelated to treatment). [c]ISL/LEN: road traffic accident (n = 1); SOC: pneumonia complicated by cardiogenic shock/cardiac arrest (n = 1), and central nervous system lymphoma (n = 1).
AE, adverse event; **DAIDS**, Division of AIDS; **ISL**, islatravir; **LEN**, lenacapavir; **QW**, once weekly; **SOC**, standard-of-care

Participant-Reported Outcomes and Adherence at Week 48





- At Week 48, most participants considered SOC more burdensome than ISL/LEN (64% vs 1%), while 78% reported greater satisfaction with ISL/LEN compared with SOC
- Mean (SD) adherence to ISL/LEN through Week 48 was 99.3% (2.96)[b] and 98.4% of participants took at least 90% of doses[c]

Participant-reported outcomes per HIV-PP-RC.[1]
[a]Data missing for 17/314 (5.4%) ISL/LEN participants. [b]On-treatment adherence (%) = [total number of tablets administered / tablets expected to be administered on treatment] × 100. [c]Adherence level denominator was the number of participants on treatment who returned at least one bottle and had calculable adherence. **HIV-PP-RC**, HIV Patient Perspective of Regimen Change; **ISL**, islatravir; **LEN**, lenacapavir; **SOC**, standard-of-care.
1. Bailey JR, et al. *J Acquir Immune Defic Syndr* 2024; 97: 286–95.

Conclusions

- Once-weekly oral ISL/LEN maintained high rates of virologic suppression (95%) at Week 48, and was noninferior to daily SOC
- No emergent resistance to ISL or LEN was detected through Week 48
- ISL/LEN was well tolerated with few participants discontinuing treatment due to adverse events
- There were no clinically meaningful changes in CD4+ T-cell counts, lymphocytes, or body weight
- Participants demonstrated high adherence to once-weekly oral ISL/LEN, were more satisfied with ISL/LEN, and found it to be less of a burden compared with daily SOC

ISL/LEN has the potential to be the first complete once-weekly oral single-tablet regimen for the treatment of HIV-1

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1; **SOC**, standard-of-care.

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Additional Resources for ISL/LEN

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ISLEND-1 Presentation Today

OAB1406LB: Week 48 results from ISLEND-1, evaluating once-weekly ISL/LEN compared with once-daily B/F/TAF

“ARTistic strategies 2: The long game” 15:00–16:00 Session room: 202