



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

- **Amy E Colson** received honoraria for a speaker's bureau and support for attending meetings and/or travel from Gilead Sciences, Inc.; and support for clinical trials (paid to their institution) from Gilead Sciences, Inc. and Merck
- **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. **Ploenchon 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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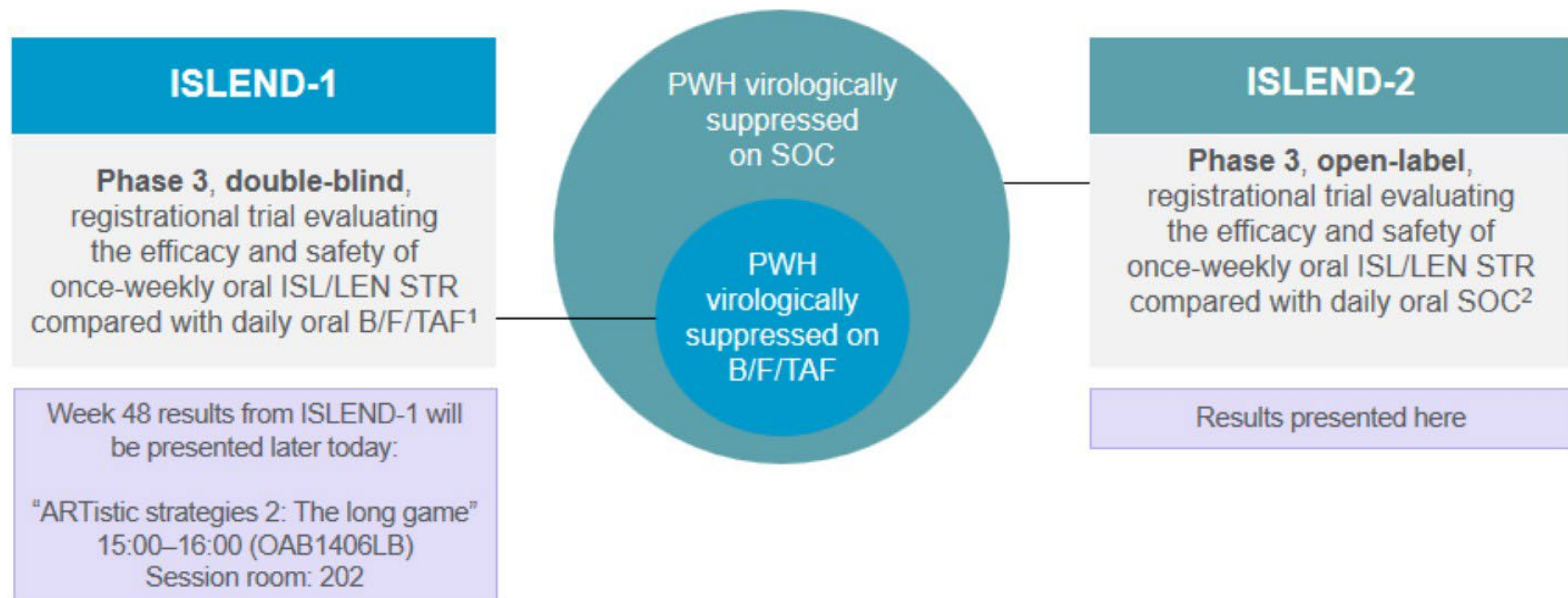
Background and Objectives

- 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 outcomes¹⁻⁴
- 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 dosing⁸⁻¹⁰
- 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

ISL/LEN Phase 3 Development Program

PWH With Virologic Suppression



Study Design: Global Trial at 100 Sites¹

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

Eligibility criteria:

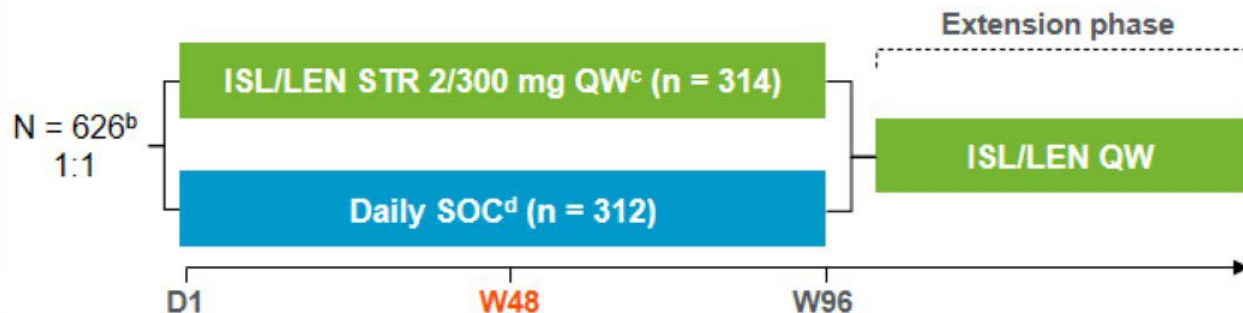
- Age ≥ 18 years
- HIV-1 RNA < 50 copies/mL for ≥ 6 months on daily oral SOC
- No prior exposure to ISL or LEN
- No history of virologic failure
- No HBV infection^a

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/ μ L)



Primary endpoint:

- HIV-1 RNA ≥ 50 copies/mL per US FDA Snapshot

Secondary endpoints:

- HIV-1 RNA < 50 copies/mL
- Change from baseline in CD4+ T-cell count
- Adverse events leading to treatment discontinuation

Exploratory endpoints

- Participant-reported outcomes
- Assessment of mutations conferring resistance

^aDefined as surface antigen positive or core antibody positive/surface antibody negative. ^bRandomized: N=634, dosed: N=626. ^cInitiation/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. ^dAll 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

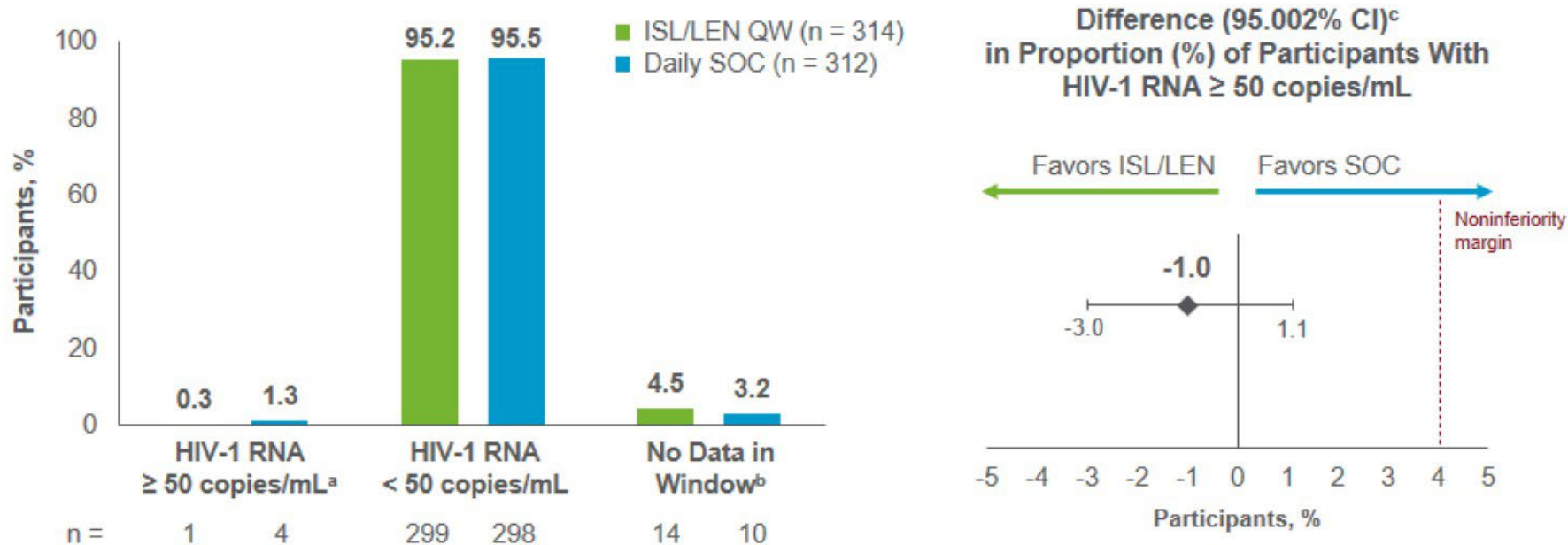
	ISL/LEN QW (n = 314)	Daily SOC (n = 312)	Total (N = 626)
Age, years, median (IQR)	52 (42–60)	53 (43–61)	52 (42–60)
Age ≥ 65 years, n (%)	47 (15)	42 (13)	89 (14)
Assigned female at birth, n (%)	105 (33)	106 (34)	211 (34)
Race, n (%) ^a			
White	130 (41)	134 (43)	264 (42)
Black	94 (30)	99 (32)	193 (31)
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)

^aLocal 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%]).

^bCategory 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

^aHIV-1 RNA ≥ 50 copies/mL in Week 48 window: ISL/LEN, n = 1; SOC, n = 4. ^bDiscontinued 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. ^cDifference (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/ μ L; SOC, 0.10×10^3 cells/ μ L)
- No participants discontinued due to decreases in CD4+ T-cell or lymphocyte counts

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 ($\geq 2\%$ 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

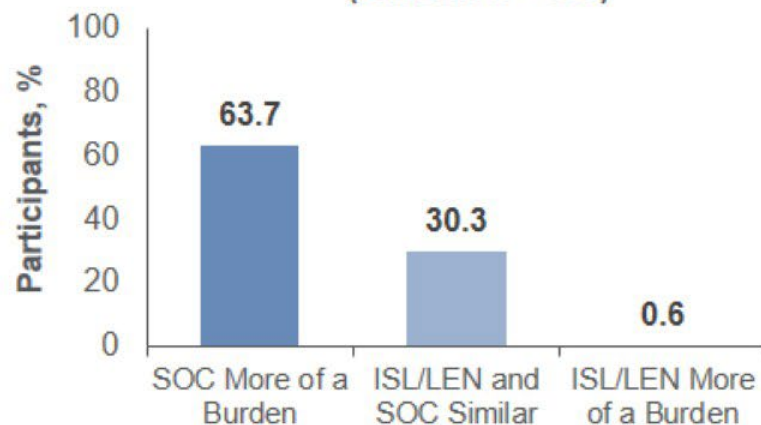
Severity grades were defined by the DAIDS Toxicity Grading Scale, version 2.1.

^aISL/LEN: seizure (n = 1). ^bISL/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). ^cISL/LEN: road traffic accident (n = 1); SOC: pneumonia complicated by cardiogenic shock/cardiac arrest (n = 1), and central nervous system lymphoma (n = 1).

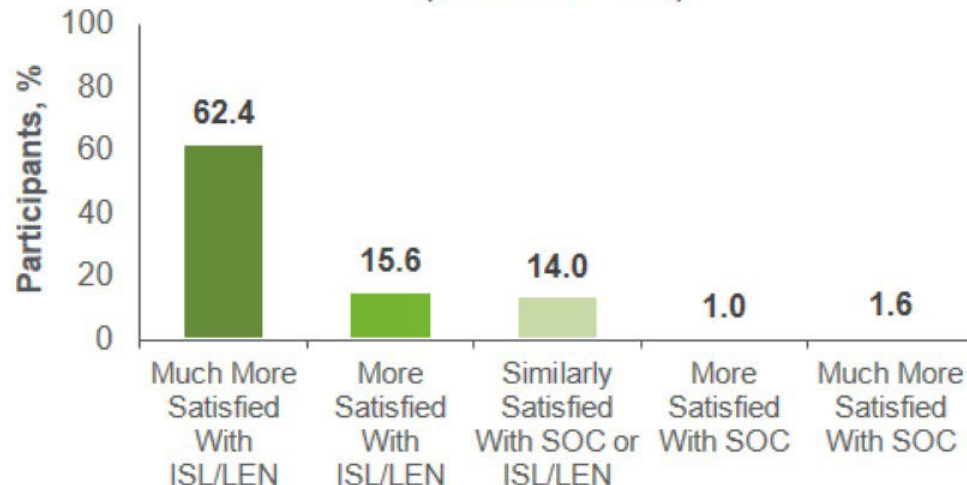
AE, adverse event; DAIDS, Division of AIDS; ISL, islatravir; LEN, lenacapavir; QW, once weekly; SOC, standard-of-care

Participant-Reported Outcomes and Adherence at Week 48

Regimen More of a Burden
(ISL/LEN n = 314)^a



More Satisfied With Regimen
(ISL/LEN n = 314)^a



- 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

^aData missing for 17/314 (5.4%) ISL/LEN participants. ^bOn-treatment adherence (%) = [total number of tablets administered / tablets expected to be administered on treatment] × 100. ^cAdherence 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

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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