OAB1406LB

Once-Weekly Oral Islatravir/Lenacapavir (ISL/LEN) Versus Daily Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) in Virologically Suppressed Adults With HIV-1: Week 48 Results of the ISLEND-1 Phase 3 Trial

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Disclosures

- **Jürgen K Rockstroh** received consulting fees from Boehringer Ingelheim, Merck Sharp & Dohme, and ViiV Healthcare; honoraria from AbbVie, Gilead Sciences, Inc., Janssen, Merck Sharp & Dohme, and ViiV Healthcare; participated on a data safety monitoring board or advisory board for Merck Sharp & Dohme and ViiV Healthcare; and holds an unpaid position on the European AIDS Clinical Society governing board

- **Moti N Ramgopal** received consulting fees from Gilead Sciences, Inc., Shionogi, and ViiV Healthcare; and honoraria from AbbVie, Gilead Sciences, Inc., Merck Sharp & Dohme, and ViiV Healthcare. **Adrian Curran Fabregas** received grants (paid to their institution) from Gilead Sciences, Inc. and ViiV Healthcare; honoraria from Cilag, Gilead Sciences, Inc., Janssen, Merck Sharp & Dohme, and ViiV Healthcare; and support to attend meetings and/or travel from Gilead Sciences, Inc. **Malcolm Hedgcock** received honoraria and support to attend meetings and/or travel from, and participated on a data safety monitoring board or advisory board for, Gilead Sciences, Inc., Merck Sharp & Dohme, and ViiV Healthcare. **Kimberly A Workowski** received grants (paid to their institution) from Gilead Sciences, Inc. **Sylvie Ronot-Bregigeon** received support to attend meetings and/or travel from Gilead Sciences, Inc. and ViiV Healthcare. **Isabel Cassetti** received honoraria from Gador Argentina, Gilead Sciences, Inc., and Merck; and support to attend meetings and/or travel from Gador Argentina and Richmond Argentina. **Cynthia Brinson** received honoraria and support to attend meetings and/or travel from Gilead Sciences, Inc. **Samir K Gupta** received grants (paid to their institution) from ViiV Healthcare; and consulting fees from Gilead Sciences, Inc. and ViiV Healthcare. **Chien-Ching Hung** received grants (paid to their institution), honoraria, and consulting fees from Gilead Sciences, Inc. **Mark O'Reilly** received honoraria from Gilead Sciences, Inc.; support to attend meetings and/or travel from Gilead Sciences, Inc., Janssen, and ViiV Healthcare; and holds unpaid positions as an ASHM Board Member and on the Australian ARV guidelines committee. **Jihad Slim** received honoraria from Gilead Sciences, Inc., Merck, Thera, and ViiV Healthcare. **Hiroyuki Gatanaga** received honoraria from Gilead Sciences, Inc., Merck Sharp & Dohme, and ViiV Healthcare. **Peter Shalit** received grants (paid to their institution) and consulting fees from Gilead Sciences, Inc., GSK, and Merck; honoraria from Gilead Sciences, Inc. and GSK; and participated on a data safety monitoring board or advisory board for Gilead Sciences, Inc., GSK, and Merck. **Shan-Yu Liu**, **Fadi Shihadeh**, **Reneé-Claude Mercier**, **Hadas Dvory-Sobol**, and **Martin S Rhee** are employees and shareholders of Gilead Sciences, Inc. **Stephanie Klopfer**, **Nidhi Patel**, **Melissa Shaughnessy**, and **Cyril Llomoso** are employees and shareholders of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. (Rahway, NJ, USA). **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. **Chloe Orkin** received grants (paid to their institution) from Gilead Sciences, Inc., Merck Sharp & Dohme, and ViiV Healthcare; consulting fees and honoraria from Bavarian Nordic, Gilead Sciences, Inc., GSK, Merck Sharp & Dohme, and ViiV Healthcare; support to attend meetings and/or travel from Bavarian Nordic, Gilead Sciences, Inc., and ViiV Healthcare; and holds an unpaid position on the governing council of the International AIDS Society

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 B/F/TAF in people with HIV-1 who were virologically suppressed on B/F/TAF

What did you find?

- Switching to once-weekly oral ISL/LEN was well tolerated and maintained a high rate of virologic suppression; efficacy was noninferior to that of B/F/TAF 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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B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir.

Background and Objectives

- Once-weekly oral antiretrovirals have the potential to address pill fatigue and adherence challenges related to daily oral treatment for HIV-1[1-3]
- The combination of islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor,[4,5] and lenacapavir (LEN), a capsid inhibitor,[6] 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 long-acting oral combination therapy due to their long half-lives that allow for weekly dosing[7-9]
- In a prior Phase 2 study in virologically suppressed PWH, once-weekly oral ISL + LEN was well tolerated, and maintained high efficacy through Week 96[10,11]

We present Week 48 analyses of the Phase 3 ISLEND-1 study evaluating the switch to once-weekly oral ISL/LEN from once-daily oral B/F/TAF in virologically suppressed PWH

1. Claborn KR, et al. *Psychol Health Med*. 2015;20(3):255-65. 2. Nachega JB, et al. *Clin Infect Dis*. 2014;58(9):1297-307. 3. Graham SM, et al. *J Int AIDS Soc*. 2023;26 Suppl 2(Suppl 2):e26099. 4. Michailidis E, et al. *J Biol Chem*. 2014;289(35):24533-48. 5. Salie ZL, et al. *Proc Natl Acad Sci USA*. 2016;113(33):9274-9. 6. Link JO, et al. *Nature*. 2020;584(7822):614-8. 7. Segal-Maurer S, et al. *N Engl J Med*. 2022;386(19):1793-803. 8. Matthews RP, et al. *Clin Transl Sci*. 2021;14(5):1935-44. 9. Diamond TL, et al. *Antimicrob Agents Chemother*. 2024;68(7):e0033424. 10. Colson AE, et al. *Ann Intern Med*. 2026;179(2):168-76. 11. Colson AE, et al. *Top Antivir Med*. 2026;34(1):583 [Abstract 516].
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1.

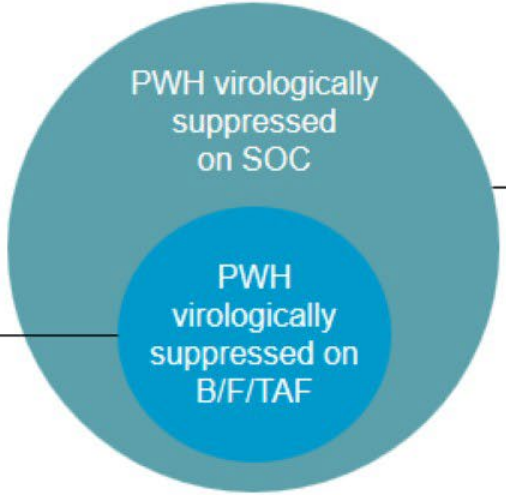
ISL/LEN Phase 3 Development Program

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]

Results presented here



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]

Week 48 results from ISLEND-2 were presented earlier today:

"AIDS 2026: Co-Chairs' Choice"
10:30–11:30 (OAX1106LB)

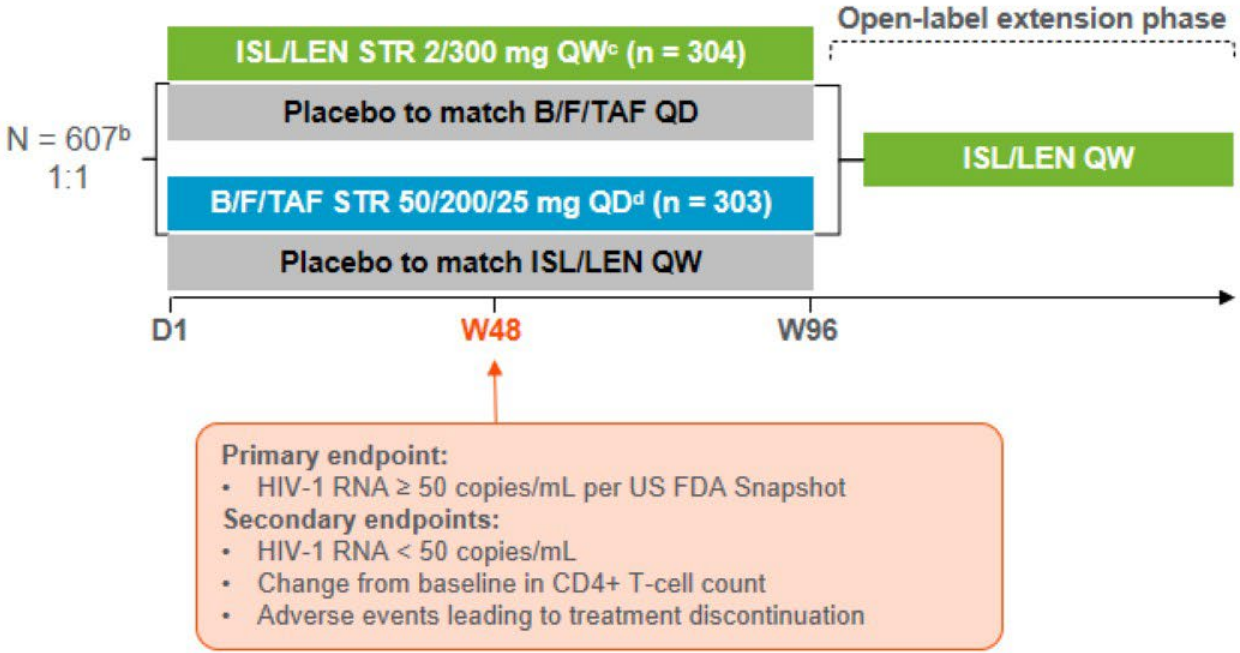
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1; **SOC**, standard of care; **STR**, single-tablet regimen.
1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06630286 (accessed June 30, 2026). 2. ClinicalTrials.gov.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

Study Design: Global trial at 106 sites[1]

ISLEND-1: Phase 3, double-blind, active-controlled noninferiority study in virologically suppressed PWH

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

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



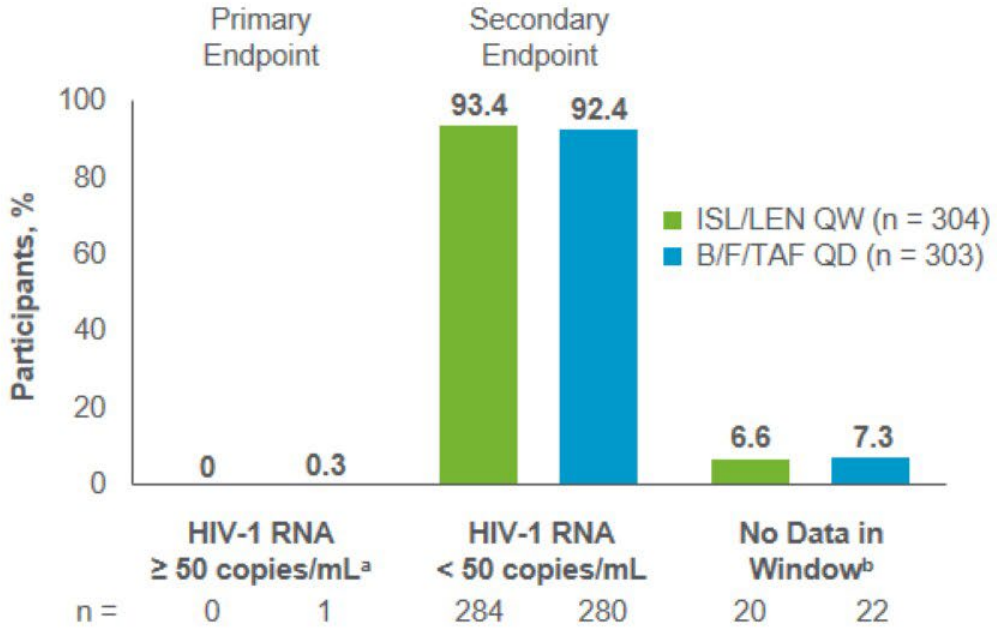
[a]Positive HBsAg or positive HBcAb and negative HBsAb. [b]Randomized: N=609; dosed: N=607. [c]Participants received a loading (initiation) dose of ISL/LEN 0.5/300 mg × 2 tablets administered orally on Days 1 and 2, then STR ISL/LEN 2/300 mg tablet administered orally once weekly from Day 8, without regard to food, plus matching B/F/TAF placebo. [d]Participants continued B/F/TAF 50/200/25 mg tablet administered orally once daily, without regard to food, and received matching ISL/LEN placebo (loading dose and weekly treatment). **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **D**, Day; **HBcAb**, hepatitis B core antibody; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1; **QD**, once daily; **QW**, once weekly; **STR**, single-tablet regimen; **W**, Week. 1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06630286 (accessed April 16, 2026).

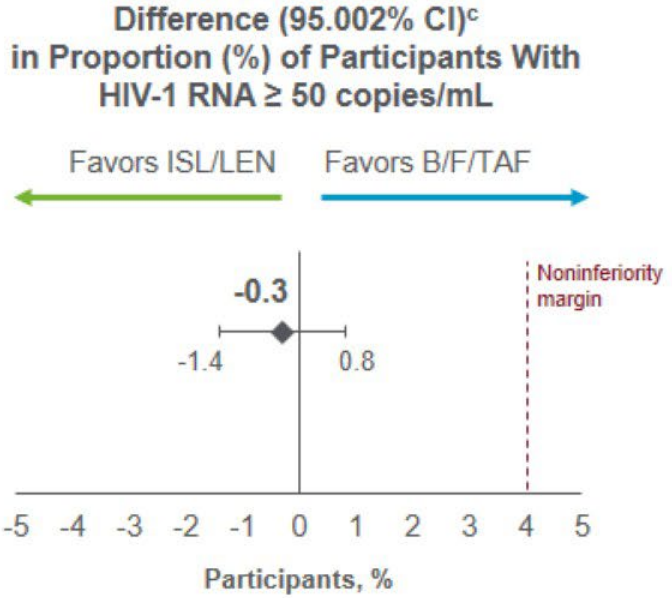
Baseline Demographic and Clinical Characteristics

	ISL/LEN QW (n = 304)	B/F/TAF QD (n = 303)
Age, years, median (IQR)	49 (38–60)	48 (38–60)
Age ≥ 50 years, n (%)	151 (50)	143 (47)
Age ≥ 65 years, n (%)	52 (17)	40 (13)
Assigned female at birth, n (%)	67 (22)	58 (19)
Gender identity, n (%)		
Cisgender man or woman	299 (98)	296 (98)
Transgender, gender nonbinary, or gender nonconforming	5 (2)	7 (2)
Race, n (%)[a]		
White	148 (49)	128 (42)
Black	89 (29)	100 (33)
Asian	32 (11)	33 (11)
Other[b]	20 (7)	25 (8)
Ethnicity: Hispanic, or Latine, n (%)[a]	73 (24)	87 (29)
BMI, kg/m^2, mean (SD)	28.3 (6.4)	28.0 (6.4)
Body weight, kg, mean (SD)	84.8 (19.3)	83.2 (17.5)
CD4+ T-cell count, cells/µL, mean (SD)	739 (289.2)	745 (319.3)
≥ 500 cells/µL, n (%)	241 (79)	240 (79)
Lymphocyte count × 10^3 cells/µL, mean (SD)	1.86 (0.52)	1.90 (0.62)

[a]Local regulators did not allow collection of race in 32 participants (ISL/LEN, n = 15 [5%]; B/F/TAF, n = 17 [6%]) or ethnicity in 25 participants (ISL/LEN, n = 11 [4%]; B/F/TAF, n = 14 [5%]).
[b]Category includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, and Other.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BMI**, body mass index; **ISL**, islatravir; **LEN**, lenacapavir; **QD**, once daily; **QW**, once weekly.

Virologic Outcomes (FDA Snapshot) at Week 48

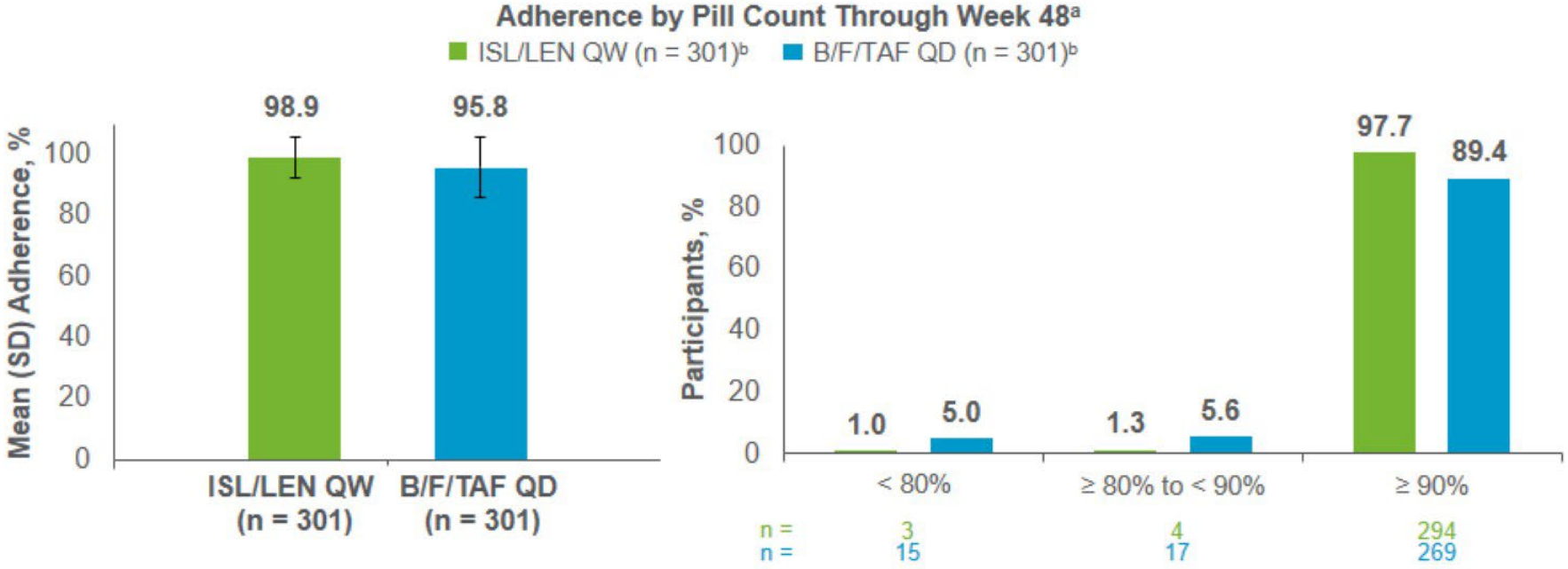




- Efficacy of once-weekly oral ISL/LEN was noninferior to that of once-daily B/F/TAF
- No emergent resistance to ISL or LEN was detected through Week 48

[a]Discontinued study drug due to other reasons and last available HIV-1 RNA was ≥ 50 copies/mL: B/F/TAF, n = 1. [b]Discontinued study drug due to adverse event: ISL/LEN, n = 6; B/F/TAF, n = 4. Discontinued study drug due to other reasons and last available HIV-1 RNA was < 50 copies/mL: ISL/LEN, n = 13; B/F/TAF, n = 15. Missing data during analysis window but still on study drug: ISL/LEN, n = 1; B/F/TAF, n = 3. [c]Difference in proportion of participants (ISL/LEN minus B/F/TAF) and two-sided 95.002% CI were constructed based on stratum-adjusted Mantel-Haenszel proportion adjusted by geographic region (US vs non-US); NI was achieved if the upper bound of the 95.002% CI was <4%. **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir; **NI**, noninferiority; **QD**, once daily; **QW**, once weekly.

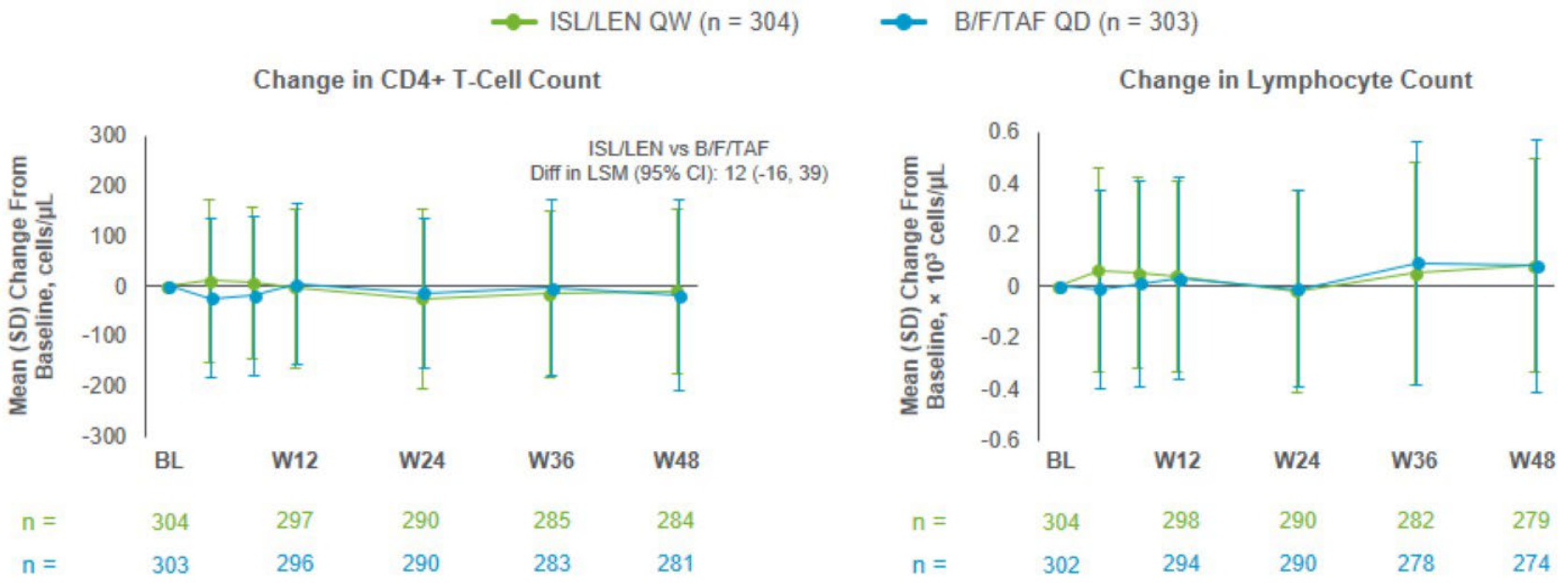
Adherence to Study Treatment



The proportion of participants with adherence rates of ≥ 90% was 98% in the ISL/LEN group and 89% in the B/F/TAF group[b]

On-treatment adherence (%) = [total number of tablets administered / tablets expected to be administered on treatment] × 100.
[a]Adherence data relate to active treatment only (not placebo): adherence to weekly treatment for ISL/LEN; adherence to daily treatment for B/F/TAF, error bars represent the SD.
[b]Denominator for this analysis was the number of participants who returned at least one bottle and had calculable adherence.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir; **QD**, once daily; **QW**, once weekly.

CD4+ T-cell and Lymphocyte Count Changes Through Week 48



- There were no between-group differences in CD4+ T-cell count
- A similar mean increase in absolute lymphocyte count was observed in both groups at Week 48
- No participants discontinued due to a decrease in CD4+ T-cell or lymphocyte counts

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BL**, baseline; **Diff**, difference; **ISL**, islatravir; **LEN**, lenacapavir; **LSM**, least squares mean; **QD**, once daily; **QW**, once weekly; **W**, Week.

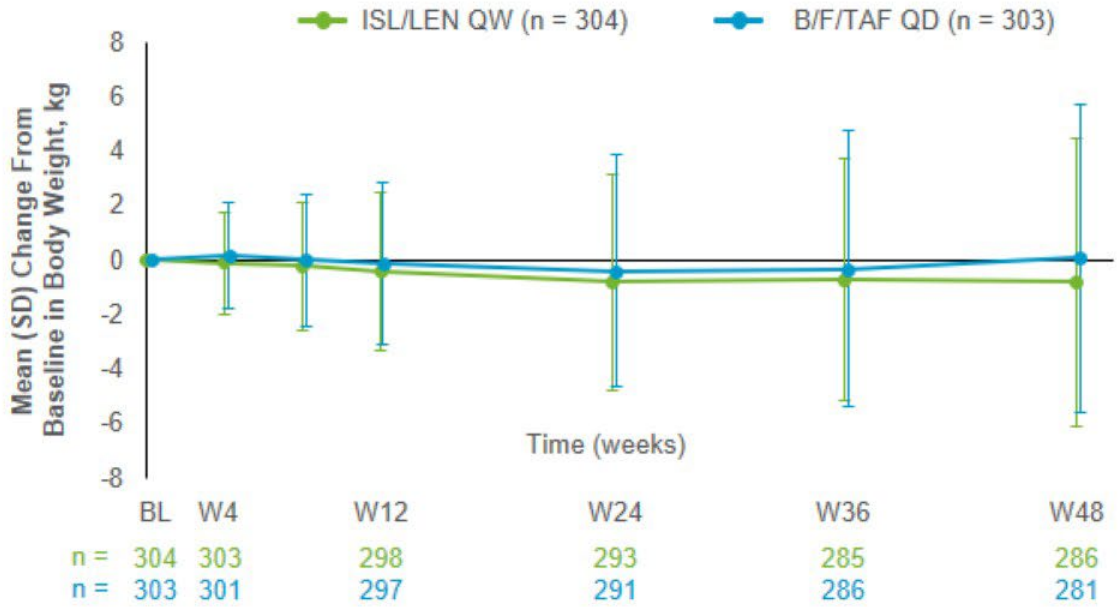
Safety Profile Overview

Participants, n (%)	ISL/LEN QW (n = 304)	B/F/TAF QD (n = 303)
Any AE	241 (79)	238 (79)
Grade ≥ 3	22 (7)	22 (7)
Treatment-related AEs	41 (13)	40 (13)
Most common treatment-related AEs (≥ 2% in the ISL/LEN group)		
Nausea	9 (3)	10 (3)
Headache	9 (3)	8 (3)
Dizziness	6 (2)	0
Serious AEs	16 (5)	14 (5)
AEs leading to study drug discontinuation[a]	6 (2)	5 (2)
Deaths	0	0

- There was one treatment-related serious AE: maculopapular rash (Grade 3) in an individual with prior history of asthma and drug hypersensitivity
- One participant (unvaccinated) discontinued treatment due to an AE of hepatitis B (Grade 2)

Severity grades were defined by the DAIDS Toxicity Grading Scale, version 2.1.
[a]Four of these 11 participants had treatment-related AEs leading to treatment discontinuation: myalgia and arthralgia (n = 1), rash maculo-papular (n = 1), arthralgia (n = 1), and brain fog and disturbance in attention (n = 1). Because of the potential for functional unblinding of investigators due to the low frequency of these AEs, they are reported without treatment-group attribution.
AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **DAIDS**, Division of AIDS; **ISL**, islatravir; **LEN**, lenacapavir; **QD**, once daily; **QW**, once weekly.

Change From Baseline in Body Weight Through Week 48



There were no clinically meaningful changes in body weight from baseline to Week 48 in either treatment group (ISL/LEN: -0.8 [±5.28] kg; B/F/TAF: 0.1 [±5.65] kg)

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BL**, baseline; **ISL**, islatravir; **LEN**, lenacapavir; **QD**, once daily; **QW**, once weekly; **W**, Week.

Conclusions

- Once-weekly oral ISL/LEN maintained high rates of virologic suppression (93%) at Week 48 and was noninferior to daily B/F/TAF
- No emergent resistance to ISL or LEN was detected through Week 48
- CD4+ T-cell counts and lymphocyte counts were stable through Week 48, with no clinically meaningful changes and no discontinuations due to declines
- Once-weekly oral ISL/LEN was generally well tolerated, with few participants discontinuing treatment due to adverse events

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.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Weekly Oral Islatravir–Lenacapavir for HIV-1 Treatment

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