ORIGINAL ARTICLE

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

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ABSTRACT

BACKGROUND

Once-daily, single-tablet regimens have transformed care for persons living with human immunodeficiency virus type 1 (HIV-1); however, challenges to adherence continue to limit effective treatment. Long-acting oral-drug combinations could offer new options with less frequent dose administration.

METHODS

We conducted a phase 3, double-blind, randomized, active-controlled, noninferiority trial in 12 countries to evaluate the efficacy and safety of a switch to once-weekly oral islatravir–lenacapavir (ISL/LEN) from once-daily oral bictegravir–emtricitabine–tenofovir alafenamide (B/F/TAF) in adults in whom HIV-1 had been virologically suppressed for at least 6 months while they were receiving B/F/TAF. Participants were assigned in a 1:1 ratio to receive once-weekly ISL/LEN (2 mg/300 mg) or to continue once-daily B/F/TAF for 96 weeks; all received matched placebo for the alternative regimen. The primary end point was the percentage of participants with an HIV-1 RNA level of 50 copies per milliliter or higher at week 48, as determined by the Food and Drug Administration–defined snapshot algorithm. Noninferiority was determined at a margin of 4 percentage points.

RESULTS

A total of 607 participants underwent randomization; 304 were assigned to the ISL/LEN group and 303 to the B/F/TAF group. A total of 21% of the participants were women, 31% were Black, 26% were Hispanic or Latine, and 15% were 65 years of age or older. At week 48, an HIV-1 RNA level of 50 copies per milliliter or higher was reported in no participants in the ISL/LEN group and 1 (0.3%) in the B/F/TAF group (difference, −0.3 percentage points; 95.002% confidence interval [CI], −1.4 to 0.8); an HIV-1 RNA level of less than 50 copies per milliliter was reported in 284 (93.4%) and 280 (92.4%), respectively (difference, 1.0 percentage point, 95% CI, −3.2 to 5.2). The mean change in the CD4+ T-cell count at week 48 was −10 cells per microliter with ISL/LEN and −18 cells per microliter with B/F/TAF (least-squares mean difference, 12 cells per microliter; 95% CI, −16 to 39). The trial regimen was discontinued owing to adverse events in 6 participants (2.0%) in the ISL/LEN group and 5 (1.7%) in the B/F/TAF group; serious adverse events occurred in 16 (5.3%) and 14 (4.6%), respectively.

CONCLUSIONS

Among persons with virologically suppressed HIV-1, once-weekly oral ISL/LEN was noninferior to once-daily B/F/TAF in maintaining HIV viral load suppression. (Funded by Gilead Sciences and Merck Sharp and Dohme; ISLEND-1 ClinicalTrials.gov number, NCT06630286.)

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*A list of the ISLEND-1 trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 29, 2026, at NEJM.org.

DOI: 10.1056/NEJMoa2607973

Once-daily, single-tablet, combination antiretroviral therapy has transformed care for persons living with human immunodeficiency virus (HIV). Such therapy warrants sustained adherence to minimize the risk of treatment failure, onward transmission, and emergence of drug resistance; however, once-daily dose administration can lead to "pill fatigue" (i.e., mental, emotional, or behavioral weariness associated with taking medication on a regular basis).[1-4] To mitigate these concerns, evaluation of additional treatment options, including treatments with less frequent dose administration and different modes of administration, is needed.[5-9] Persons living with HIV have shown interest in longer-acting treatments with either injectable or oral agents, with a preference for the latter.[6,8,10]

Islatravir, a nucleoside reverse-transcriptase translocation inhibitor,[11,12] is approved for use in combination with doravirine for the treatment of HIV type 1 (HIV-1) infection.[13] Lenacapavir is a first-in-class selective inhibitor of HIV-1 capsid function.[14,15] Twice-yearly subcutaneous lenacapavir is approved for use in adults with multidrug resistance and limited options for treatment in combination with antiretroviral therapy,[16,17] as well as for the prevention (preexposure prophylaxis) of HIV-1 infection.[18,19] Both islatravir and lenacapavir have pharmacokinetic profiles that support once-weekly oral administration.[12,20]

Given their distinct mechanisms of action and resistance profiles, islatravir in combination with lenacapavir (ISL/LEN) has the potential to be a long-acting, once-weekly, single-tablet oral regimen for the treatment of HIV-1. In a phase 3 trial, we evaluated the efficacy and safety of a switch to ISL/LEN from once-daily bictegravir–emtricitabine–tenofovir alafenamide (B/F/TAF) in adults with virologically suppressed HIV-1, with a planned follow-up period of 96 weeks. Here, we report the results for the primary efficacy end point and for the secondary and safety end points at week 48.

METHODS

TRIAL DESIGN

This double-blind, randomized, active-controlled, noninferiority trial (ISLEND-1) was conducted at 106 sites in 12 countries. The primary objective was to evaluate the efficacy of switching therapy to a once-weekly, single-tablet, oral regimen with ISL/LEN from once-daily B/F/TAF (a guideline-recommended single-tablet regimen[21]), as compared with continuing therapy with B/F/TAF, in persons with virologically suppressed HIV-1 (Fig. 1A).

PARTICIPANTS AND PROCEDURES

Participants were eligible if they were adults (≥18 years of age) with virologically suppressed HIV-1 (a documented plasma HIV-1 RNA level of <50 copies per milliliter) for at least 6 months before screening while they were receiving B/F/TAF and had no previous exposure to islatravir or lenacapavir, no previous virologic failure, and no active hepatitis B virus (HBV) infection. Full inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Participants who became pregnant during the course of the trial were allowed to continue treatment after an in-depth risk–benefit discussion and consent signing, provided that they did not plan to breast-feed. According to the diversity plan for the trial (Table S2), every effort was made to recruit a diverse population of participants according to sex, race and ethnic group, region, and age.

Participants who met the eligibility criteria were randomly assigned in a 1:1 ratio to switch to once-weekly ISL/LEN therapy or to continue therapy with once-daily B/F/TAF. Randomization was stratified according to geographic region (United States vs. outside the United States) at randomization and CD4+ cell count (<200 cells, 200 to <350 cells, 350 to <500 cells, and ≥500 cells per microliter) at screening. The participants in the ISL/LEN group received two tablets, each containing 0.5 mg of islatravir (initiation dose) and 300 mg of lenacapavir (loading dose), administered orally on days 1 and 2, followed by one tablet with 2 mg of islatravir and 300 mg of lenacapavir, administered orally once weekly, without regard to food intake, starting on day 8. The participants in the B/F/TAF group received one tablet with 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide, administered orally once daily from day 1 without regard to food intake. Participants in both treatment groups received matching placebo for the alternative treatment, including matched placebo for the ISL/LEN initiation–loading dose in the B/F/TAF group.

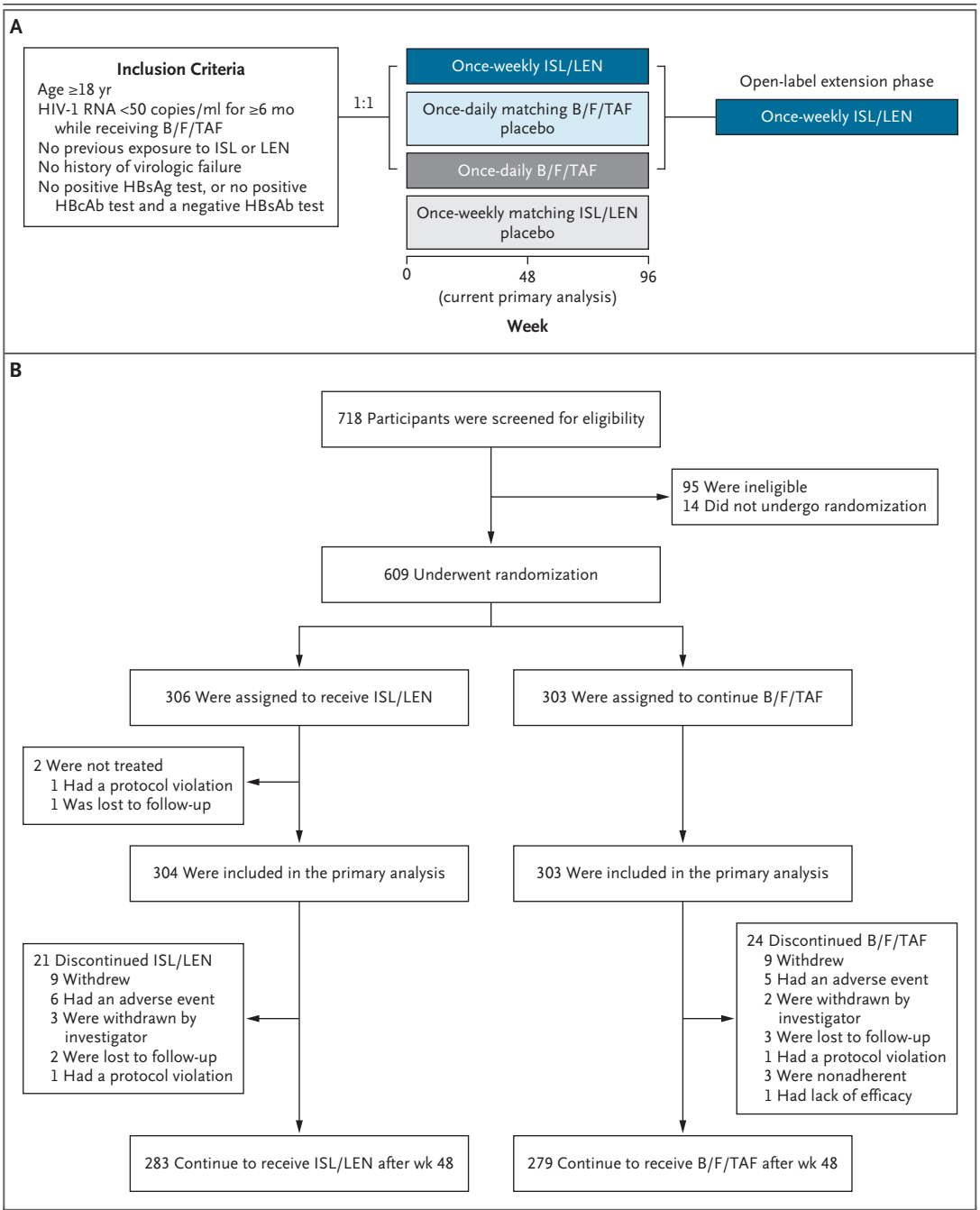

Figure 1. Trial Design and Participant Flow through the Trial.

Panel A shows a diagram of the trial design. Panel B shows the screening, randomization, and follow-up of the participants. A total of 57 participants did not meet inclusion criteria, and 50 participants met exclusion criteria (the reasons, not mutually exclusive, are shown in Table S3 in the Supplementary Appendix). The reasons for not undergoing randomization were withdrawal of consent (9 participants), loss to follow-up (3 participants), and other reason (2 participants). The reasons for withdrawal by the investigator were extended time off treatment, personal issues, immunocompromise due to chemotherapy, use of investigational product not allowed at behavioral health facility, and nonadherance (in 1 participant each). B/F/TAF denotes bictegravir–emtricitabine–tenofovir alafenamide, HBcAb hepatitis B core antibody, HBsAb hepatitis B surface antibody, HBsAg hepatitis B surface antigen, and ISL/LEN islatravir–lenacapavir.

Participants were seen for follow-up at weeks 4, 8, and 12 and subsequently every 12 weeks. Telephone visits occurred at day 2 to confirm that the initiation–loading dose was taken and at day 8 to confirm the start of weekly dose administration and the participant's understanding of missed dose recommendations. Laboratory assessments and assessments for adverse events occurred at each in-person visit. Additional details regarding the trial procedures and frequency of assessments are provided in the protocol, available at NEJM.org.

END POINTS

The primary efficacy end point was the percentage of participants with an HIV-1 RNA level of 50 copies per milliliter or higher at week 48, as determined by the Food and Drug Administration (FDA)–defined snapshot algorithm.[22] Secondary efficacy end points at week 48 were an HIV-1 RNA level of less than 50 copies per milliliter and the change from baseline in CD4+ T-cell count.

Safety end points included absolute lymphocyte counts and discontinuation of ISL/LEN owing to adverse events. The safety analysis included adverse events that began on or after the start date of the trial treatment and up to 60 days after permanent discontinuation of ISL/LEN or up to 30 days after permanent discontinuation of B/F/TAF, as well as adverse events that led to premature discontinuation of the trial treatment.

The trial is ongoing, and the data will remain blinded until week 96. Because of the potential for functional unblinding owing to rare events (when the treatment assignment can be inferred even though the trial is formally blinded), detailed characterization of individual adverse events is limited. Aggregate data are presented, and all safety events were reviewed in full by an independent data and safety monitoring committee whose members had access to unblinded data.

Exploratory end points included evaluation of resistance-associated mutations in participants with confirmed virologic failure and changes in patient-reported outcomes. Confirmed virologic failure was defined as an HIV-1 RNA level of 50 copies per milliliter or higher at any postbaseline visit, with confirmation at a subsequent assessment or at the last visit while receiving treatment; participants with an HIV-1 RNA level of 200 copies per milliliter or higher underwent genotypic and phenotypic resistance testing.

TRIAL OVERSIGHT

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines, and all applicable laws and regulatory requirements. The protocol was approved by the institutional review board or ethics committee at each trial site. The trial sites, along with the trial investigators, are listed in the Supplementary Appendix. All the participants provided written informed consent. The sponsors (Gilead Sciences and Merck Sharp and Dohme) developed the trial protocol, collected the data, monitored the conduct of the trial, and performed the statistical analyses.

All the authors contributed to the critical review of the manuscript, approved the final version, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (see the Supplementary Appendix). Medical writing and editing support for earlier versions of the manuscript was funded by the sponsors and was performed in accordance with Good Publication Practice guidelines.

STATISTICAL ANALYSIS

Assuming that virologic failure would occur in 2% of the participants in each treatment group at week 48, we estimated that a sample of 600 participants would provide the trial with at least 93% power to show noninferiority of ISL/LEN to B/F/TAF, at a one-sided alpha level of 0.0249, with respect to the percentage of participants with HIV-1 RNA level of 50 copies per milliliter or higher at week 48. The noninferiority margin was set at 4 percentage points on the basis of FDA guidance.[22] Analyses by an independent data-monitoring committee were planned to take place after 50% of the participants had completed week 12 and 24 visits and when all participants had either completed their week 48 visit or had prematurely discontinued trial treatment during the blinded phase. An alpha penalty of 0.00001 was applied for each planned evaluation by the data monitoring committee (weeks 12 and 24). Therefore, the one-sided alpha level for the primary end point was adjusted to 0.02499 (corresponding to a 95.002% confidence interval).

The primary efficacy analysis included all the participants who had undergone randomization and received at least one dose of the trial treatment, and the participants were grouped accord-

ing to the treatment to which they had been assigned. Between-group differences in the percentage of participants with an HIV-1 RNA level of 50 copies per milliliter or higher, along with the two-sided 95.002% confidence intervals, were calculated on the basis of stratum-adjusted Mantel–Haenszel proportions, with adjustment for geographic region (United States vs. outside the United States). Additional analysis methods are described in the Methods section in the Supplementary Appendix.

Analyses were conducted with SAS software, version 9.4 (SAS Institute). Further details on the statistical analyses are provided in the protocol and statistical analysis plan (available with the protocol).

RESULTS

PARTICIPANTS

Between October 9, 2024, and April 22, 2025, a total of 718 participants were screened, and 607 underwent randomization and received treatment (304 were assigned to the ISL/LEN group and 303 to the B/F/TAF group); 45 discontinued treatment (Fig. 1B). Reasons for screen failures are shown in Table S3.

The demographic and clinical characteristics of the participants were generally similar in the treatment groups (Table 1 and Table S4). The median age of the participants was 49 years (interquartile range, 38 to 60), 92 (15.2%) were 65 years of age or older, 125 (20.6%) were designated as female at birth, and 12 (2.0%) identified as transgender, gender nonbinary, or gender nonconforming. Among the 607 participants, most were White (276 [45.5%]), Black (189 [31.1%]), or Asian (65 [10.7%]), and 160 participants (26.4%) were of Hispanic or Latine ethnicity. The mean (±SD) CD4+ T-cell count at baseline was 742±304.4 cells per microliter; 5.1% of the participants had an M184V/I mutation at baseline. The representativeness of the trial population is described in Table S5.

EFFICACY

At week 48, an HIV-1 RNA level of 50 copies per milliliter or higher was reported in no participants in the ISL/LEN group and in 1 participant (0.3%) in the B/F/TAF group (difference, −0.3 percentage points; 95.002% confidence interval [CI], −1.4 to 0.8), which met the prespecified noninferiority criteria for the primary end point (Fig. 2). The results of the per-protocol analysis and other sensitivity analyses were generally consistent with those of the primary analysis (Table S6). At week 48, an HIV-1 RNA level of less than 50 copies per milliliter was reported in 284 participants (93.4%) in the ISL/LEN group and in 280 participants (92.4%) in the B/F/TAF group (difference, 1.0 percentage point; 95.002% CI, −3.2 to 5.2), which showed noninferiority of ISL/LEN to B/F/TAF according to the FDA-defined snapshot algorithm (Fig. 2).

At week 48, resistance to either islatravir or lenacapavir did not develop in any trial participant. In the ISL/LEN group, the efficacy results were similar regardless of the presence or absence of an M184V/I mutation at baseline, with an HIV-1 RNA level of less than 50 copies per milliliter reported in 12 of 13 participants (92.3%) with the mutation and in 254 of 271 participants (93.7%) without the mutation.

The mean CD4+ T-cell count at baseline was 739±289.2 cells per microliter in the ISL/LEN group and 745±319.3 cells per microliter in the B/F/TAF group; at week 48, the counts were 725±279.2 cells per microliter and 722±309.8 cells per microliter, respectively. The mean change in the CD4+ T-cell count at week 48 was −10 cells per microliter with ISL/LEN and −18 cells per microliter with B/F/TAF (least-squares mean difference, 12 cells per microliter; 95% CI, −16 to 39) (Fig. 3A). The results were consistent when stratified according to sex (Fig. S1). No participants discontinued treatment owing to a decreased CD4+ T-cell count.

Adherence to the trial regimen up to week 48, as assessed according to pill count, was 98.9±6.71% in the ISL/LEN group and 95.8±9.74% in the B/F/TAF group (Fig. S2A). The percentage of participants with at least 95% adherence to the trial regimen was 96.0% in the ISL/LEN group and 80.4% in the B/F/TAF group (Fig. S2B).

SAFETY

Adverse events were reported in 241 participants (79.3%) in the ISL/LEN group and in 238 participants (78.5%) in the B/F/TAF group (Table 2). The most common adverse events were upper respiratory tract infection, nasopharyngitis, and diarrhea in the ISL/LEN group and upper respiratory

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Once-Weekly ISL/LEN (N=304)	Once-Daily B/F/TAF (N=303)	Total (N=607)
Age			
Median (IQR) — yr	49 (38–60)	48 (38–60)	49 (38–60)
Range — yr	20–87	21–87	20–87
Distribution			
≥50 yr — no. (%)	151 (49.7)	143 (47.2)	294 (48.4)
≥65 yr — no. (%)	52 (17.1)	40 (13.2)	92 (15.2)
Female sex assigned at birth — no. (%)	67 (22.0)	58 (19.1)	125 (20.6)
Median weight (IQR) — kg	80.5 (72.0–95.2)	79.8 (71.4–93.0)	80.0 (71.7–94.0)
Gender identity — no. (%)			
Cisgender man or woman	299 (98.4)	296 (97.7)	595 (98.0)
Transgender, gender nonbinary, or gender nonconforming	5 (1.6)	7 (2.3)	12 (2.0)
Race — no. (%)†			
White	148 (48.7)	128 (42.2)	276 (45.5)
Black	89 (29.3)	100 (33.0)	189 (31.1)
Asian	32 (10.5)	33 (10.9)	65 (10.7)
Hispanic or Latine ethnic group — no. (%)†	73 (24.0)	87 (28.7)	160 (26.4)
Geographic region — no. (%)			
United States	182 (59.9)	183 (60.4)	365 (60.1)
Outside the United States	122 (40.1)	120 (39.6)	242 (39.9)
HIV-1 RNA level ≥50 copies/ml — no. (%)	5 (1.6)	5 (1.7)	10 (1.6)
CD4+ T-cell count — cells/μl	739±289.2	745±319.3	742±304.4
CD4+ T-cell count <200 cells/μl — no. (%)	3 (1.0)	6 (2.0)	9 (1.5)
Median eGFR (IQR) — ml/min‡	101.6 (81.3–125.8)	101.0 (82.8–121.6)	101.0 (82.0–124.2)
Absolute lymphocyte count — cells/μl§	1860±524	1900±617	1880±572
History of AIDS — no. (%)	13 (4.3)	8 (2.6)	21 (3.5)
Median duration of HIV-1 from diagnosis (IQR) — yr¶	14.2 (7.3–23.0)	14.2 (7.3–23.0)	14.2 (7.3–23.0)
Median duration of HIV-1 treatment (IQR) — yr‖	12.3 (7.1–19.3)	13.1 (7.1–19.1)	12.3 (7.1–19.2)

* Plus–minus values are means ±SD. Full details of the demographic and clinical characteristics of the participants at baseline are provided in Table S4 in the Supplementary Appendix. AIDS denotes acquired immunodeficiency syndrome, B/F/TAF bictegravir–emtricitabine–tenofovir alafenamide, HIV-1 human immunodeficiency virus type 1, IQR interquartile range, and ISL/LEN islatravir–lenacapavir.
† Race and Hispanic or Latine ethnic group were reported by the participants.
‡ The estimated glomerular filtration rate (eGFR) was calculated with the use of the Cockcroft–Gault formula.
§ Data were not available for 1 participant in the B/F/TAF group.
¶ Data were not available for 2 participants in the ISL/LEN group.
‖ Data were not available for 5 participants in the ISL/LEN group and 5 participants in the B/F/TAF group.

tract infection, headache, and diarrhea in the B/F/TAF group (Table S7). Adverse events that were deemed by the investigators to be related to treatment were reported in 41 participants (13.5%) in the ISL/LEN group and in 40 participants (13.2%) in the B/F/TAF group (Table S8). Treatment-related adverse events occurring in at least 2% of participants were headache (in 9 participants [3.0%] in the ISL/LEN group and in 8 participants [2.6%] in the B/F/TAF group) and nausea (in 9 [3.0%] and 10 [3.3%], respectively). Among the participants who had any adverse event or any treatment-related adverse event, the majority had adverse events of grade 1 or 2 (in 90.8% of those with any adverse

event and in 98.8% of those with any treatment-related adverse event).

Because of the potential for functional unblinding owing to rare events in this ongoing trial, some specific adverse events with very low frequency are not attributed to a treatment group. Adverse events of grade 3 or higher were reported in 22 participants (7.2%) in the ISL/LEN group and in 22 participants (7.3%) in the B/F/TAF group, and among these, 1 participant with a history of asthma and drug allergies had an event that was considered to be treatment-related (grade 3 maculopapular rash). Grade 3 adverse events that were reported in more than 1 participant were abdominal pain, asthma, and syncope, occurring in 1 participant (<1%) each in both treatment groups; no grade 3 adverse events occurred in more than 1 participant in each treatment group (Table S9).

Serious adverse events were reported in 16 participants (5.3%) in the ISL/LEN group and in 14 participants (4.6%) in the B/F/TAF group (Table S10); as mentioned previously, 1 of these participants (0.2% of all participants) had an event that was considered to be treatment-related (grade 3 maculopapular rash). A total of 6 participants (2.0%) in the ISL/LEN group and 5 participants (1.7%) in the B/F/TAF group discontinued treatment owing to adverse events; one adverse event that led to treatment discontinuation occurred in more than 1 participant (arthralgia was reported in 2 participants [0.3% of all participants]) (Table S11). Among all the participants, an incident case of HBV infection was reported on day 183 in a participant who had not received the HBV vaccine. The participant had seroconversion and was positive for hepatitis B surface antigen at week 24 and was also positive for total hepatitis B core antibody at a subsequent unscheduled visit and discontinued treatment. The participant had elevated liver enzyme levels (alanine aminotransferase, aspartate aminotransferase, and total bilirubin), which normalized by the day 60 follow-up visit. No deaths were reported in either treatment group (Table 2).

Grade 3 or 4 abnormalities in laboratory values were reported in 52 participants (17.2%) in the ISL/LEN group and in 72 participants (23.8%) in the B/F/TAF group (Table S12). The most frequent grade 3 or 4 abnormalities in laboratory values in the ISL/LEN group were an increased direct bilirubin level, occurring in 22 participants (7.3%) (in 19 participants [6.3%] in the B/F/TAF group); decreased creatinine clearance, occurring in 12 participants (4.0%) (in 34 participants [11.3%] in the B/F/TAF group); and glycosuria, occurring in 9 participants (3.0%) (in 9 participants [3.0] in the B/F/TAF group). The mean change in lymphocyte count from baseline to week 48 was $0.08\pm0.416\times10^3$ cells per microliter in the ISL/LEN group and $0.08\pm0.493\times10^3$ cells per microliter in the B/F/TAF group (Fig. S3). No participants discontinued treatment owing to a decrease in lymphocyte count. The change or percentage change in body weight from baseline to week 48 was similar in the two groups in the overall population and when stratified according to sex (Fig. S4).

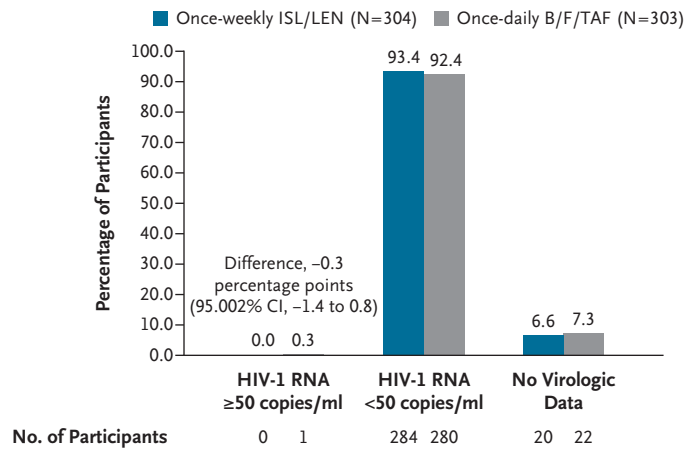

Figure 2. Virologic Outcomes at Week 48.

Two-sided 95.002% confidence intervals were constructed on the basis of stratum-adjusted Mantel–Haenszel proportions, with adjustment according to geographic region (United States vs. outside the United States). The percentage of participants with a human immunodeficiency virus type 1 (HIV-1) RNA level of 50 copies per milliliter or higher at week 48 (primary end point) was determined by the Food and Drug Administration–defined snapshot algorithm. Among the participants who had an HIV-1 RNA level of less than 50 copies per milliliter at 48 weeks, 1 participant discontinued the assigned trial treatment (B/F/TAF) owing to "other reasons" and had a last available HIV-1 RNA level of 50 copies per milliliter or higher. Among the participants who had no virologic data, 6 in the ISL/LEN group and 4 in the B/F/TAF group had discontinued the trial regimen owing to an adverse event; 13 and 15, respectively, had discontinued the trial regimen for other reasons and had a last available HIV-1 RNA level of less than 50 copies per milliliter; and 1 and 3, respectively, had missing data during the analysis window but were still receiving the trial treatment. "Other reasons" for discontinuing the trial regimen included withdrawal by the investigator, withdrawal by the participant, loss to follow-up, nonadherence to the trial regimen, and pregnancy.

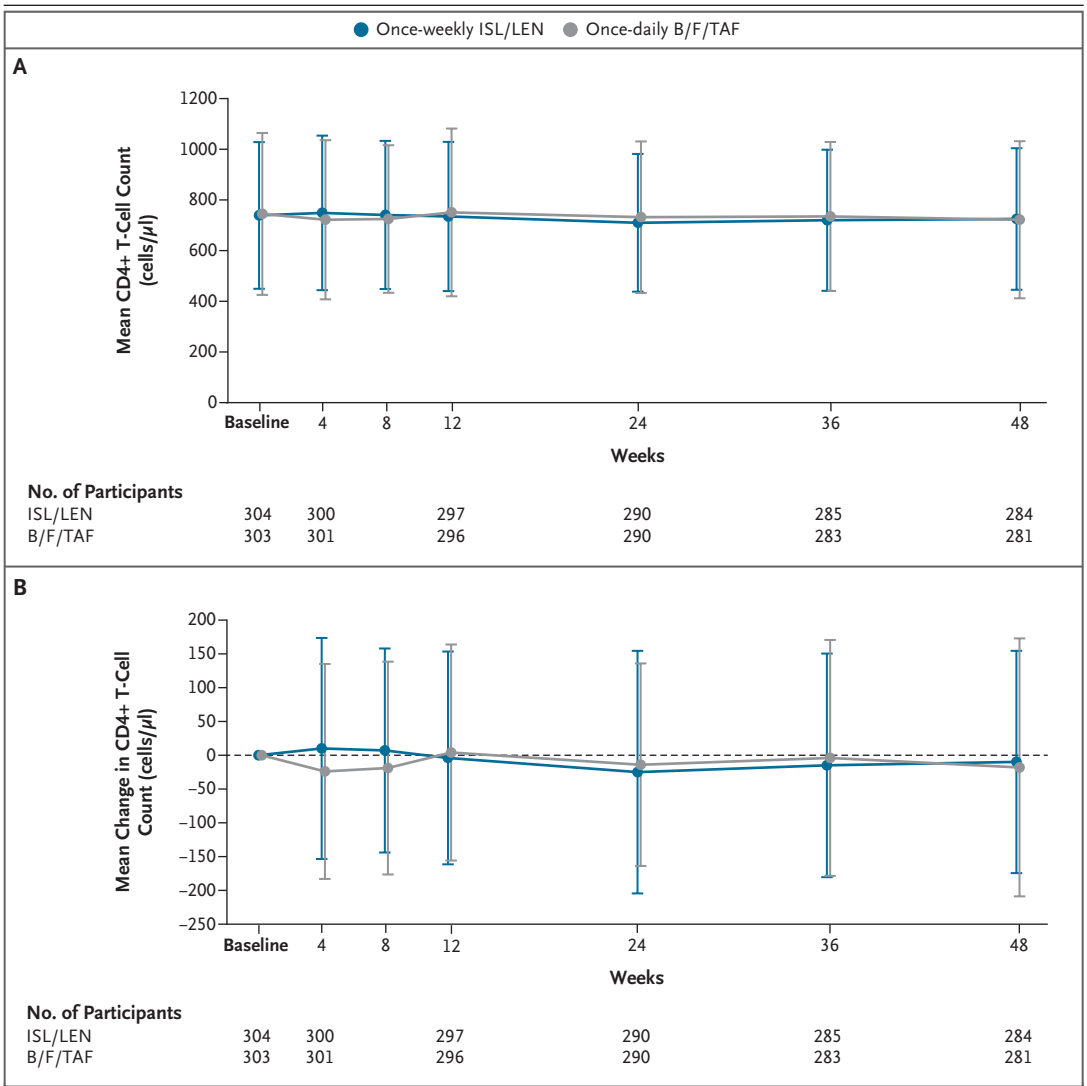

Figure 3. CD4+ T-Cell Count through Week 48.

Panel A shows the mean absolute CD4+ T-cell counts and Panel B the change from baseline in CD4+ T-cell counts through week 48. I bars indicate the standard deviation.

DISCUSSION

Although once-daily, single-tablet regimens have reshaped the treatment of HIV-1, there remains a need for treatment options that can provide more flexibility and decrease pill fatigue. In this phase 3 trial, the once-weekly, single-tablet, oral ISL/LEN regimen showed noninferior efficacy to guideline-recommended, once-daily, oral B/F/TAF, with virologic suppression occurring in a high percentage of participants (93.4%) at week 48. Likewise, in the open-label phase 3 ISLEND-2 trial, switching to ISL/LEN was noninferior to continuing the current standard regimen, with virologic suppression being maintained with ISL/LEN in 95.2% of the participants at week 48.[23]

No safety signals were observed, with few participants having adverse events of grade 3 or higher or serious adverse events or adverse events leading to premature discontinuation of treatment. Although dose-dependent decreases in CD4+ T-cell and total lymphocyte counts were previously noted with daily islatravir doses of 0.75 mg or higher,[24-26] these reductions were not observed in trials that used a lower dose of islatravir, including a phase 2 study of islatravir in

Table 2. Safety Summary.

Adverse Event*	Once-Weekly ISL/LEN (N=304)	Once-Daily B/F/TAF (N=303)	Unattributed†
	no. of participants (%)		*no. of participants (% in either group)*
Adverse event of any grade	241 (79.3)	238 (78.5)	
Adverse event of grade ≥3	22 (7.2)	22 (7.3)	
Treatment-related adverse event of any grade	41 (13.5)	40 (13.2)	
Treatment-related adverse event of grade ≥3			1 (0.3)
Serious adverse event	16 (5.3)	14 (4.6)	
Treatment-related serious adverse event			1 (0.3)‡
Adverse event leading to discontinuation of trial treatment	6 (2.0)	5 (1.7)	
Treatment-related adverse event leading to discontinuation of trial treatment			4 (1.3)
Death	0	0	

* The safety analysis included adverse events that began on or after the start date of the trial treatment and up to 60 days after permanent discontinuation of ISL/LEN or up to 30 days after permanent discontinuation of B/F/TAF, as well as adverse events that led to premature discontinuation of the trial treatment. Median exposure was 58.3 weeks (IQR, 53.3 to 65.6) among the participants in the ISL/LEN group and 58.3 weeks (IQR, 53.3 to 65.3) among those in the B/F/TAF group. Treatment relatedness was determined by the investigators while the treatment-group assignments remained blinded. Treatment-related adverse events were subsequently tabulated according to treatment group for the safety analysis.

† The events included in this column are reported without treatment-group attribution because of their very low frequency and potential for functional unblinding.

‡ A mild grade 1 papular rash localized to the chest and back was first reported on day 17. The participant was hospitalized on day 65 for pneumonia with asthma exacerbation and hypoxia and was treated with levofloxacin and glucocorticoids. The participant had a transient reduction in the rash during hospitalization while receiving systemic glucocorticoids; however, the rash recurred and worsened after discontinuation of glucocorticoid treatment. A serious adverse event of grade 3 maculopapular rash was documented on day 72. The trial regimen was permanently discontinued on day 86. The rash persisted after discontinuation of the trial regimen but showed a gradual reduction. The participant was given a prescription for daily doxycycline starting on day 121, and continued reduction was noted. At day 134, the rash was downgraded to a nonserious, grade 2 event, which was ongoing at the end of trial follow-up.

combination with lenacapavir.[27,28] In the current trial, we did not observe such decreases, and CD4+ T-cell and lymphocyte counts remained stable until the data cutoff at week 48. As such, these findings support the safety of the current weekly 2-mg dose of islatravir. Because ISL/LEN does not have any anti-HBV activity, the possibility of acquisition or reactivation of HBV infection is an important consideration. Hence, participants with active HBV infection were excluded from our trial, which is consistent with guidelines for regimens that do not contain tenofovir.[21,29] One participant, who was unvaccinated for HBV, had an incident case of HBV infection. The longer-term safety data may provide further valuable insight beyond the week 48 data presented here.

A once-weekly oral regimen may offer an alternative for persons who prefer less frequent dose administration over daily oral regimens or oral regimens over injectable regimens. Despite the blinded design of ISLEND-1, which meant that participants received both once-daily and once-weekly oral tablets, adherence to ISL/LEN and B/F/TAF over 48 weeks was 99% and 96%, respectively, in this trial. Because participants had virologically suppressed HIV-1 at baseline, which implies high adherence to their existing B/F/TAF treatment, this group of participants may not be fully representative of the real-world population, in which adherence challenges are common.[30] Unlike long-acting injectable agents, a once-weekly oral treatment is not conducive to direct monitoring of adherence through clinic visits; nevertheless, it may be amenable to structured adherence support, which has been shown to improve adherence.[31,32]

Although long-acting injectable combinations are approved or under development for the treatment of HIV-1,[33] injections are not a treatment approach preferred by all; the use of injectable agents warrants clinic-based administration and may present challenges related to adherence to scheduled visits, as well as demands on health system capacity.[34] Weekly oral therapy may offer an alternative long-acting approach for persons who prefer oral administration or face barriers to injectable therapy.[8] Although we could not assess preference in our blinded trial, this variable was evaluated as an exploratory patient-reported outcome in the ISLEND-2 trial.[23]

One strength of this trial was the diversity of its population with respect to age, region, and race and ethnic group, which enhances the generalizability of these findings to persons living with HIV worldwide. In addition, B/F/TAF was selected as a comparator given its role as a first-line standard of care, as characterized by its high virologic efficacy and high barrier to resistance.[35] The blinded design strengthens internal validity and enables an unbiased evaluation of safety. The data presented here represent the week 48 analysis, and the data in the continuing trial remain blinded, thus limiting safety-related insights; safety will be better evaluated at the completion of the trial at week 96.

In this primary analysis of the ISLEND-1 trial, once-weekly ISL/LEN showed noninferior efficacy to once-daily B/F/TAF. Once-weekly ISL/LEN represents a potential treatment option for a complete, single-tablet, oral regimen for the treatment of HIV-1.

Supported by Gilead Sciences and Merck Sharp and Dohme.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the participants and their families, along with the trial investigators and staff members at the participating sites. We also thank Jared Baeten (Gilead Sciences) and Luisa M. Stamm (Merck Sharp and Dohme) for their critical review of the manuscript, and Jenna Steere and Christina Holleywood of Aspire Scientific for medical writing and editorial support on earlier versions of the manuscript.

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