Once-Weekly Islatravir Plus Lenacapavir in Virologically Suppressed PWH: Week 48 Safety, Efficacy, and Metabolic Changes

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Background

- Once-weekly (QW) oral antiretrovirals (ARVs) have the potential to address pill fatigue and adherence challenges related to daily oral treatment for HIV-1 infection[1]
- Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor[2]
  - Prior ISL studies have shown dose/exposure-related decreases in CD4+ T-cell and lymphocyte counts[3]
    - Pharmacokinetic modelling indicates such declines are not expected with the 2 mg dose chosen for this study[4]
- Lenacapavir (LEN) is a first-in-class capsid inhibitor[5]
- Both ISL and LEN have multiple mechanisms of action, potent ARV activity at low doses, and long half-lives ($t_{1/2}$) that allow for QW dosing[6–8,a]
- Primary endpoint data (Week 24) from the current, ongoing Phase 2 study (NCT05052996) were previously reported
  - Most participants (94.2%) maintained viral suppression in the QW oral ISL+LEN group[9]

Objective: To investigate the efficacy and safety of QW oral ISL+LEN in virologically suppressed people with HIV-1 (PWH) at Week 48

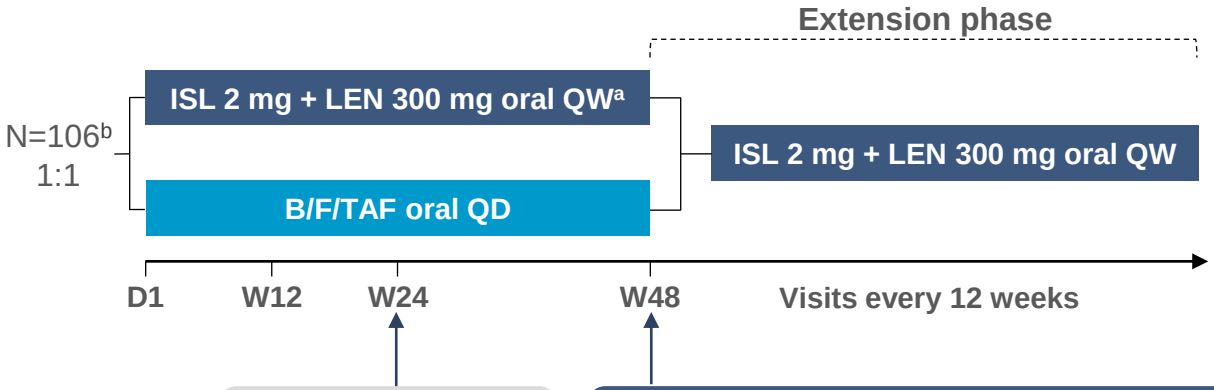
[a]LEN $t_{1/2}$=10–12 days; ISL-triphosphate $t_{1/2}$=7–9 days.

1. Claborn KR, et al. *Psychol Health Med* 2015;20:255–65; 2. Schürmann D, et al. *Lancet HIV* 2020;7:e164–72; 3. Squires K, et al. CROI 2023; Abstract 192; 4. Vargo RC, et al. CROI 2023; Poster 497; 5. Sunlenca® Prescribing Information, available at https://www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.pdf (accessed November 2024); 6. Zhang H, et al. CROI 2022; Abstract 433; 7. Shaik N, et al. AIDS 2022; Poster PESUB23; 8. Matthews R, et al. *Clin Trans Sci* 2021;14:1935–44; 9. Colson A, et al. CROI 2024; Abstract 208.

Methods

A Phase 2, Open-label, Active-Controlled Study in Virologically Suppressed PWH

Eligibility criteria
- Aged ≥18 years
- On B/F/TAF for >6 months
- HIV-1 RNA <50 c/mL for >6 months
- No history of virologic failure
- CD4+ T-cell count ≥350 cells/µl
- Lymphocyte count ≥900 cells/µl
- No HBV infection



Primary endpoint:[1]
- Proportion with HIV-1 RNA ≥50 c/mL at Week 24 per FDA Snapshot Algorithm

Secondary endpoints included in this presentation:
- Proportion with HIV-1 RNA ≥50 c/mL at Week 48
- Proportion with HIV-1 RNA <50 c/mL at Week 48
- Change from baseline in CD4+ T-cell count
- AEs leading to study drug discontinuation

Other assessments:
- Change in BMI, body weight, and adherence

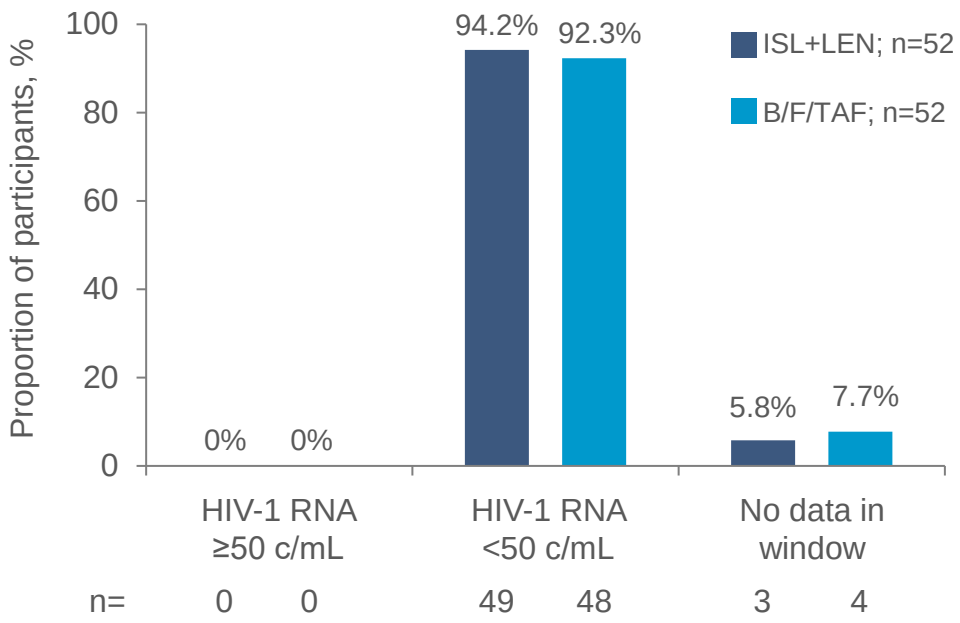
[a]600 mg of LEN was given on Day 1 and Day 2 for pharmacologic loading. [b]Randomised, N=106; dosed, n=104.
AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **BMI**, body mass index; **c/mL**, copies/ml; **D**, Day; **FDA**, Food and Drug Administration; **HBV**, hepatitis B virus; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1; **QD**, daily; **QW**, weekly; **W**, Week.
1. Colson A, et al. CROI 2024; Abstract 208.

Baseline Demographic and Disease Characteristics

	ISL+LEN (n=52)	B/F/TAF (n=52)	Total (N=104)
Median (range) age, years	40 (28–67)	40 (26–76)	40 (26–76)
Assigned female at birth, n (%)	10 (19.2)	9 (17.3)	19 (18.3)
Gender identity, n (%)			
Transgender female	1 (1.9)	0	1 (1.0)
Non-binary/third gender	0	1 (1.9)	1 (1.0)
Race, n (%)			
White	25 (48.1)	27 (51.9)	52 (50.0)
Black	21 (40.4)	16 (30.8)	37 (35.6)
Asian	2 (3.8)	1 (1.9)	3 (2.9)
American Indian or Alaska Native	1 (1.9)	2 (3.8)	3 (2.9)
Native Hawaiian or Pacific Islander	0 (0)	1 (1.9)	1 (1.0)
Other	3 (5.8)	5 (9.6)	8 (7.7)
Hispanic or Latinx ethnicity, n (%)	13 (25.0)	17 (32.7)	30 (28.8)
Mean (SD) CD4+ T-cell count, cells/μL	755 (223.6)	818 (271.3)	786 (249.5)
Mean (SD) lymphocyte count x 10^3 cells/μL	1.94 (0.445)	1.95 (0.652)	1.94 (0.556)
Median (IQR) body weight, kg	79.3 (70.4–87.4)	83.2 (76.1–92.5)	80.5 (74.4–88.7)
Median (IQR) BMI, kg/m^2	26.9 (23.8–30.0)	27.2 (25.5–29.3)	27.1 (24.5–29.4)

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BMI**, body mass index; **IQR,** interquartile range; **ISL**, islatravir; **LEN**, lenacapavir.

Virologic Outcomes at Week 48 by FDA Snapshot Algorithm



Participants with no data in window:

ISL+LEN (n=3)

- Two participants discontinued due to AEs not related to study drug
- One participant discontinued due to other reasons not related to study drug
- All participants had HIV-1 RNA <50 c/mL at study discontinuation

B/F/TAF (n=4)

- Three participants discontinued due to other reasons not related to study drug and had HIV-1 RNA <50 c/mL at study discontinuation
- One participant had missing data during window, but remained on study drug

Participants in both treatment groups maintained high rates of virologic suppression

AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **c/mL**, copies/mL; **FDA**, Food and Drug Administration; **ISL**, islatravir; **LEN**, lenacapavir.

Adverse Events

Participants, n (%)	ISL+LEN (n=52)	B/F/TAF (n=52)
Any AE	42 (80.8)	40 (76.9)
Treatment-related AE	10 (19.2)	3 (5.8)
Grade 1 or 2	10 (19.2)	3 (5.8)
≥2 participants in ISL+LEN group		
Dry mouth	2 (3.8)	0
Nausea	2 (3.8)	0
Grade 3 or 4	0	0
Serious AE	3 (5.8)[a]	0
Treatment-related	0	0
AE leading to study drug discontinuation	2 (3.8)[b]	0
Treatment-related	0	0

No Grade 3 or higher AEs, serious AEs, or AEs leading to discontinuation were considered related to the study drug by the investigator

[a]Serious AEs included large intestine perforation and renal colic (in the same participant), pneumonia, and neurologic anesthetic complication. [b]Large intestine perforation and renal colic, n=1; acute hepatitis B infection, n=1 (both participants had HIV-1 RNA <50 c/mL at study discontinuation).
AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **c/mL**, copies/mL; **ISL**, islatravir; **LEN**, lenacapavir.

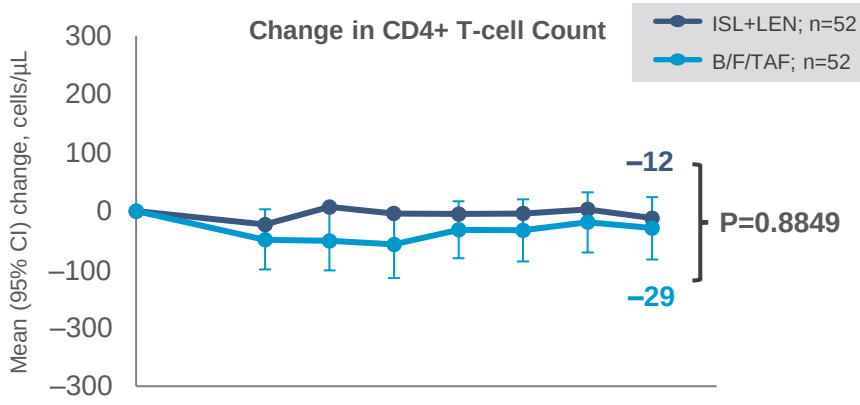
Laboratory Abnormalities

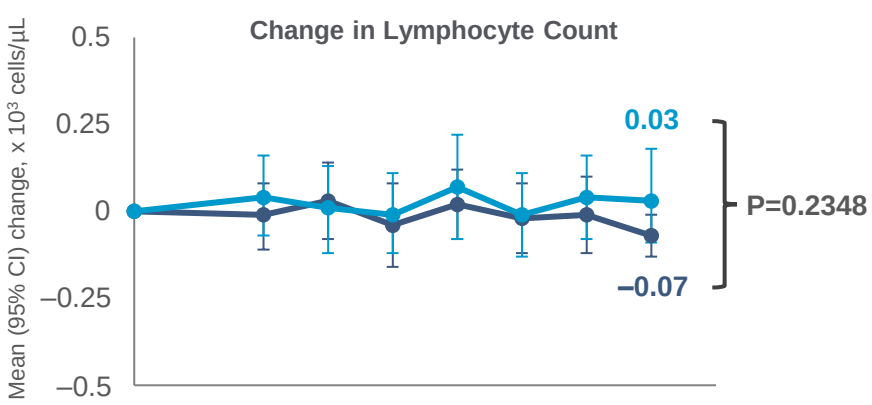
Laboratory abnormalities occurring in ≥1 participant in the ISL+LEN group, n/N (%)	ISL+LEN (n=52)	B/F/TAF (n=52)
Grade 3		
Creatinine (increased)	1/52 (1.9)	0/51
Creatinine clearance (decreased)	2/52 (3.8)	2/51 (3.9)
Non-fasting hyperglycemia	1/43 (2.3)	2/43 (4.7)
Glycosuria[a]	1/52 (1.9)	2/51 (3.9)
Hyperkalemia	1/52 (1.9)	0/51
ALT (increased)[b]	1/52 (1.9)	0/51
Grade 4		
Creatine kinase (increased)[c]	2/52 (3.8)	0/51

No Grade 3 and 4 laboratory abnormalities were clinically significant, except ALT elevation seen in a participant with acute hepatitis B

[a]Glycosuria occurred in participants with type 2 diabetes mellitus. [b]Increased ALT occurred in the participant with acute hepatitis B. [c]Increased creatinine kinase occurred after vigorous exercise in both participants.
ALT, alanine transaminase; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir.

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





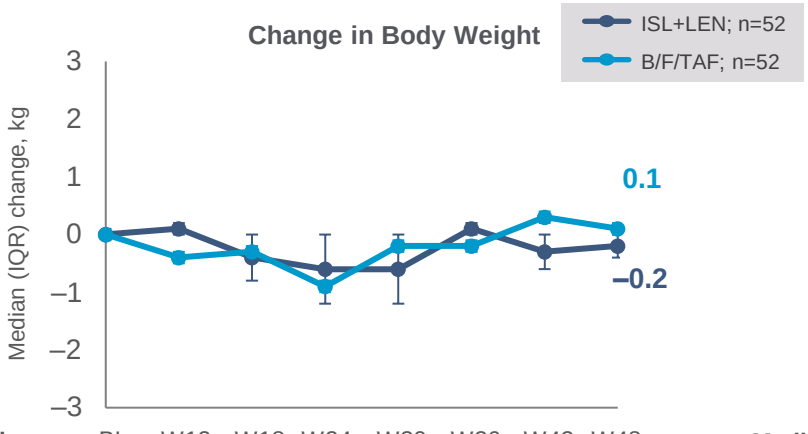
Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	755	732	766	755	754	756	761	746
B/F/TAF	818	758	767	761	785	783	797	787

Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	1.94	1.94	1.98	1.92	1.96	1.94	1.93	1.88
B/F/TAF	1.95	1.99	1.97	1.96	2.03	1.96	2.00	1.99

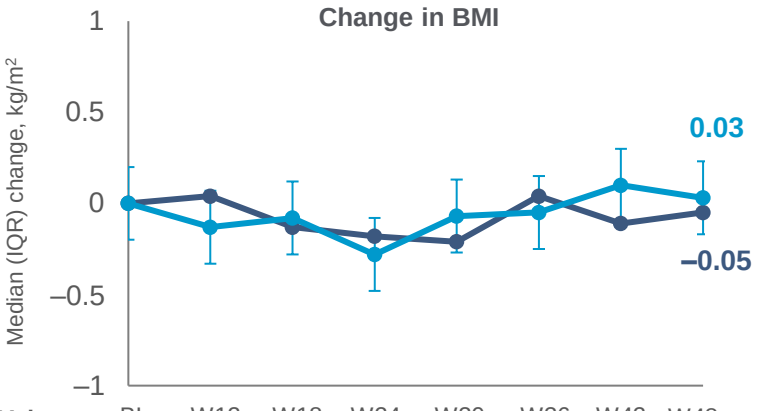
- There were no significant differences between groups in mean change from baseline in CD4+ T-cell or lymphocyte counts at Week 48
- No participants discontinued due to a decrease in CD4+ T-cell or lymphocyte counts

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

Body Weight and BMI Changes Through Week 48



Median Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	79.3	79.1	77.2	77.9	77.7	78.8	77.9	77.6
B/F/TAF	83.2	83.4	82.8	82.0	84.7	84.7	84.2	84.0

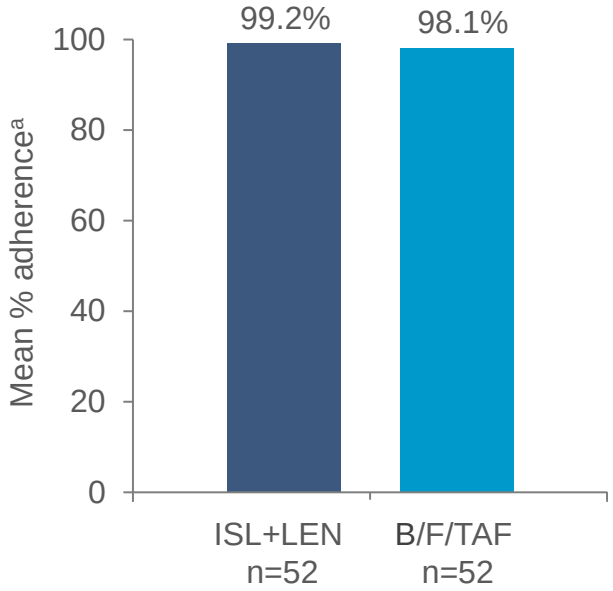


Median Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	26.9	26.8	26.9	26.6	27.2	27.1	26.6	26.7
B/F/TAF	27.2	27.4	27.3	27.3	27.4	27.9	27.6	27.7

No between-group differences in median change in body weight and BMI at Week 48

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BL**, baseline; **BMI**, body mass index; **IQR**, interquartile range; **ISL**, islatravir; **LEN**, lenacapavir; **W**, Week.

Adherence (by Pill Count) Through Week 48



Adherence was high for ISL+LEN and B/F/TAF through Week 48

[a]Adherence (%) calculated as: (total pills taken / total pills prescribed) x 100. Denominator for the adherence rate category summaries was based on number of participants who returned at least 1 bottle and had calculable adherence. For ISL, 2 capsules taken (1 mg each) was considered as a pill.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir.

Conclusions

- Weekly oral ISL+LEN maintained high rates of virologic suppression (94.2%) at Week 48 in virologically suppressed PWH
  - No participant on ISL+LEN had HIV-1 RNA ≥50 c/mL at Week 48 or at study discontinuation
- Weekly oral ISL+LEN was well tolerated, as evidenced by the absence of any treatment-related Grade ≥3 AEs or serious AEs
- There were no between-group differences in CD4+ T-cell or lymphocyte count changes from baseline through Week 48
- There were no between-group differences in body weight or BMI changes from baseline through Week 48
- Participants demonstrated high rates (99.2%) of adherence to oral weekly ISL+LEN
- The Phase 2 results support advancing the weekly oral ISL+LEN regimen to Phase 3 trials: ISLEND-1 and ISLEND-2 (NCT06630286; NCT06630299)

ISL + LEN has the potential to become the first oral weekly complete regimen for the treatment of HIV-1 infection

AE, adverse event; **BMI**, body mass index; **c/mL**, copies/ml; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1.

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