Efficacy and Safety of Weekly Islatravir Plus Lenacapavir in PWH at 24 Weeks: A Phase 2 Study

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Background

- Once weekly (QW) oral antiretrovirals (ARVs) have 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 (NRTTI)[2]
  - Prior ISL trials have shown dose/exposure-related decreases in CD4 and absolute lymphocyte counts,[3] which stabilize between Weeks 48 and 72; pharmacokinetic (PK) modeling indicates declines not expected with 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 antiretroviral activity at low doses, and long half-lives that allow for weekly dosing[6–8,a]

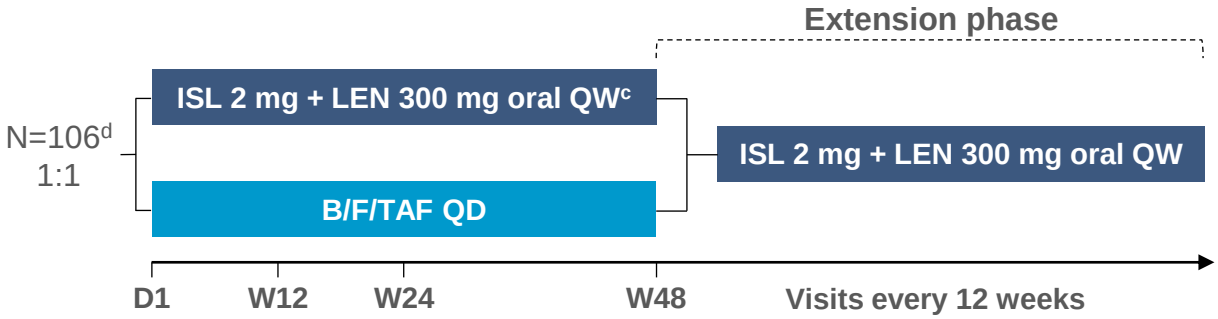
Objective: To investigate the efficacy and safety of weekly oral ISL + LEN in virologically suppressed people with HIV-1 (PWH)

[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 February 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.

Methods

A Phase 2, open-label, active-controlled study in virologically suppressed PWH[a]

Inclusion criteria
- Aged ≥18 years
- Viral load <50 c/mL on B/F/TAF[b]
- No history of virologic failure
- CD4 count ≥350 cells/µl
- Lymphocytes ≥900 cells/µl
- No HBV infection



- **Primary endpoint:** Proportion with HIV-1 RNA ≥50 c/mL at Week 24 per FDA Snapshot algorithm
- **Secondary endpoints:**
  - Proportion with HIV-1 RNA ≥50 c/mL at Weeks 12 and 48
  - Proportion with HIV-1 RNA <50 c/mL at Weeks 12, 24, and 48
  - Change from Day 1 in CD4
  - Adverse events (AE) leading to study drug discontinuation
  - PK parameters[e]
- **Exploratory endpoints[e]:**
  - Treatment-emergent resistance to ISL and LEN
  - Participant-reported outcomes

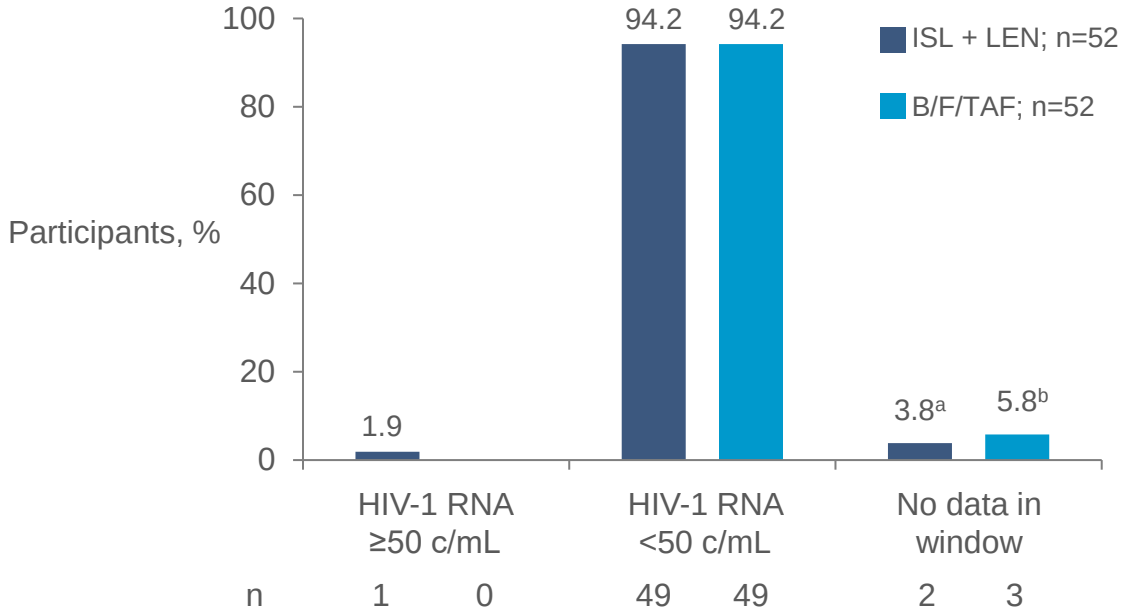
[a]NCT05052996. [b]For at least the previous 24 weeks. [c]600 mg of LEN was given on Day 1 and Day 2 for pharmacologic loading. [d]Randomized, N=106; dosed, N=104. [e]Will be presented in future presentation. **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **D**, day; **HBV**, hepatitis B virus; **ISL**, islatravir; **LEN**, lenacapavir; **PK**, pharmacokinetic; **PWH**, people with HIV-1; **QD**, daily; **QW**, weekly; **W**, week.

Baseline Demographic and Disease Characteristics

	Total (N=104)	ISL + LEN (n=52)	B/F/TAF (n=52)
Median (range) age, years	40 (26–76)	40 (28–67)	40 (26–76)
Female at birth, n (%)	19 (18.3)	10 (19.2)	9 (17.3)
Gender Identity, n (%)			
Transgender female	1 (1.0)	1 (1.9)	0
Non-binary/third gender	1 (1.0)	0	1 (1.9)
Race, n (%)			
White	52 (50.0)	25 (48.1)	27 (51.9)
Black	37 (35.6)	21 (40.4)	16 (30.8)
Asian	3 (2.9)	2 (3.8)	1 (1.9)
American Indian or Alaska Native	3 (2.9)	1 (1.9)	2 (3.8)
Native Hawaiian or Pacific Islander	1 (1.0)	0 (0)	1 (1.9)
Other	8 (7.7)	3 (5.8)	5 (9.6)
Ethnicity, Hispanic, or Latinx, n (%)	30 (28.8)	13 (25.0)	17 (32.7)
Mean (SD) CD4, cells/μL	786 (249.5)	755 (223.6)	818 (271.3)
≥500 cells/μl, n (%)	96 (92.3)	46 (88.5)	50 (96.2)
Mean (SD) absolute lymphocytes x 10^3/μL	1.94 (0.556)	1.94 (0.445)	1.95 (0.652)

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **c/mL**, copies/mL; **ISL**, islatravir; **LEN**, lenacapavir; **SD**, standard deviation

Efficacy at Week 24



Participants in both treatment groups maintained high rates of virologic suppression

[a]Discontinued due to non-drug related adverse event with HIV-1 RNA <50 c/mL at time of discontinuation, n=2. [b]Discontinued for other reason with HIV-1 RNA <50 c/mL at time of discontinuation, n=3.

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **c/mL**, copies/mL; **ISL**, islatravir; **LEN**, lenacapavir

Participant on ISL + LEN with HIV-1 RNA ≥50 c/mL at Week 24

Visit	HIV-1 RNA (c/mL)
Screening	<50
Day 1	251
Week 24	64
Week 30	<50

- Resuppressed at Week 30 without change in regimen
- Adequate levels of plasma ISL and LEN
- No emergent resistance detected
- Participant remains on study drug

c/mL, copies/mL; **ISL**, islatravir; **LEN**, lenacapavir

Safety Summary

Participants with AEs, n (%)	ISL + LEN (n=52)	B/F/TAF (n=52)
Any AE	40 (76.9)	38 (73.1)
Treatment-related AEs (TRAE)	9 (17.3)	3 (5.8)
Grade 1 and 2 TRAEs	9 (17.3)	3 (5.8)
Occurring in ≥2 ISL + LEN participants		
Dry mouth	2 (3.8)	0
Nausea	2 (3.8)	0
Grade 3 and 4 TRAEs	0	0
Serious AE	3 (5.8)[a]	0
Serious TRAE	0	0
AE leading to study drug discontinuation	2 (3.8)[b]	0
TRAE leading to discontinuation	0	0

[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.
AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir; **TRAE**, treatment-related adverse event

Grade 3/4 Laboratory Abnormalities

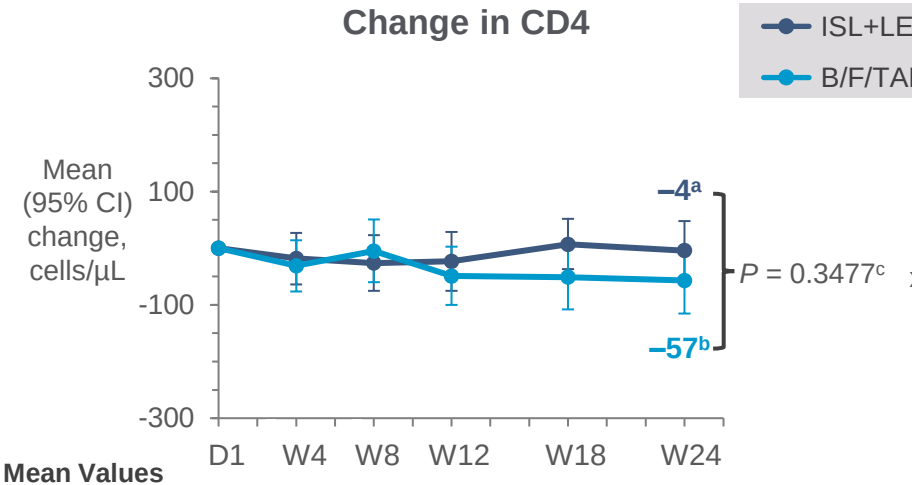
Participants with laboratory abnormalities, n (%)[a]	ISL + LEN (n=52)	B/F/TAF (n=52)
Grade 3	**5 (9.6)**	**4 (7.8)**
Increased ALT	1 (1.9)	0
Increased creatinine	1 (1.9)	0
Decreased creatinine clearance	2 (3.8)	2 (3.9)
Fasting hyperglycemia	0	1 (2.6)
Non-fasting hyperglycemia	1 (2.5)	2 (4.9)
Hyperkalemia	1 (1.9)	0
Glycosuria	1 (1.9)	2 (3.9)
Grade 4	**1 (1.9)**	**0**
Increased creatine kinase	1 (1.9)	0

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

[a]Denominator in % calculation is the total participants in each group with a postbaseline value for the given measurement type.
ALT, alanine transaminase; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir

CD4 and Absolute Lymphocyte Count Changes Through Week 24

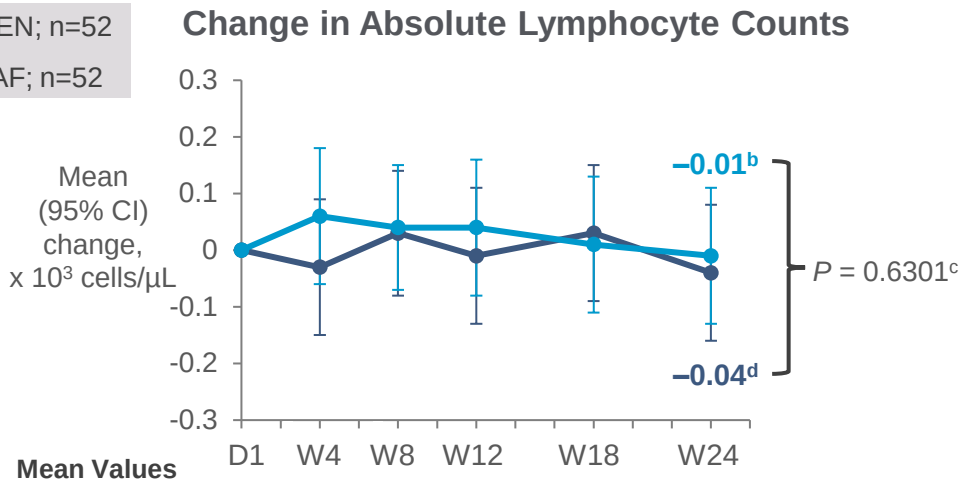
Change in CD4



Mean Values

	D1	W4	W8	W12	W18	W24
ISL + LEN	755	738	729	732	766	755
B/F/TAF	818	787	813	758	767	761

Change in Absolute Lymphocyte Counts



Mean Values

	D1	W4	W8	W12	W18	W24
ISL + LEN	1.94	1.93	1.97	1.94	1.98	1.92
B/F/TAF	1.95	1.97	1.99	1.99	1.97	1.96

- No between-group differences in CD4 and absolute lymphocyte count changes at Week 24
- No participants discontinued due to CD4 or absolute lymphocyte count decreases

[a]n=50. [b]n=50. [c]Least square mean difference. [d]n=49.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **CI**, confidence interval; **D**, day; **ISL**, islatravir; **LEN**, lenacapavir; **SD**, standard deviation **W**, Week

Conclusions

- Oral weekly ISL + LEN maintained high rates of virologic suppression (94.2%) at Week 24 in virologically suppressed PWH
- Oral weekly ISL + LEN was well tolerated, as demonstrated by the absence of any treatment-related Grade 3-4/serious AEs
- There were no between group differences in CD4 or absolute lymphocyte count changes, and no discontinuations due to CD4 or absolute lymphocyte count decreases
- The study is ongoing; additional longer-term data will be presented at a later date

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

AE, adverse event; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1

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