Oral Weekly Islatravir Plus Lenacapavir in Virologically Suppressed People with HIV-1: 96 Week Outcomes from a Phase 2 Study

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Background

- Once-weekly oral antiretroviral (ARV) therapy may provide an alternative to daily oral therapy for people with HIV-1 (PWH), with potential benefits such as improved adherence and reduced pill burden[1]
- The combination of islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor[2], and lenacapavir (LEN), a capsid inhibitor[3], is being developed as a complete once-weekly oral HIV-1 treatment
  - Both ISL and LEN have multiple mechanisms of action, potent ARV activity at low doses, and long half-lives that allow for weekly dosing[4-6]
- In this Phase 2 study (NCT05052996), weekly oral ISL+LEN maintained high rates of virologic suppression (94.2%) at Week 48 in virologically suppressed PWH[7]; participants randomised to ISL+LEN had the option to continue into the extension phase after 48 weeks

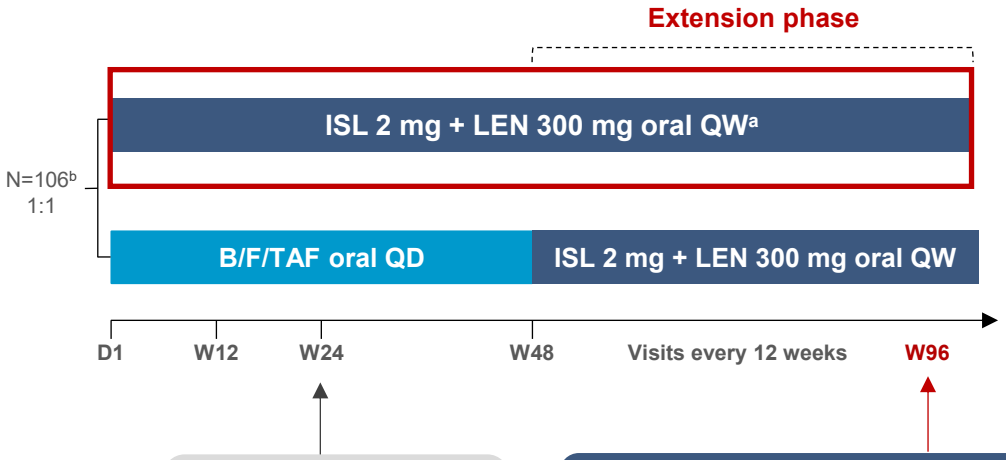
Objective: To report efficacy and safety of continuous ISL+LEN through 2 years of treatment

No participant on ISL+LEN had HIV-1 RNA ≥50 c/mL at Week 48 or at study discontinuation.
ARV, antiretroviral; **c/mL**, copies/mL; **ISL**, islatravir; **LEN**, Lenacapavir; **PWH**, people with HIV-1.
1. Claborn KR, et al. *Psychol Health Med.* 2015; 20(3):255-65; 2. Schürmann D et al. *Lancet HIV.* 2020;7:e164–72; 3. Squires K, et al. CROI 2023; Abstract 192; 4. Zhang H, et al. CROI 2022; Abstract 433; 5. Shaik N, et al. AIDS 2022; Poster PESUB23; 6. Matthews R, et al. *Clin Trans Sci.* 2021;14:1935–44; 7. Colson A, et al. IDWeek 2024; Abstract 577.

Methods

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 ≥0.9x10^3 cells/μL
- No HBV infection



Primary endpoint:[1]

- Proportion with HIV-1 RNA ≥50 c/mL at Week 24 per FDA Snapshot Algorithm

Endpoints included in this presentation:

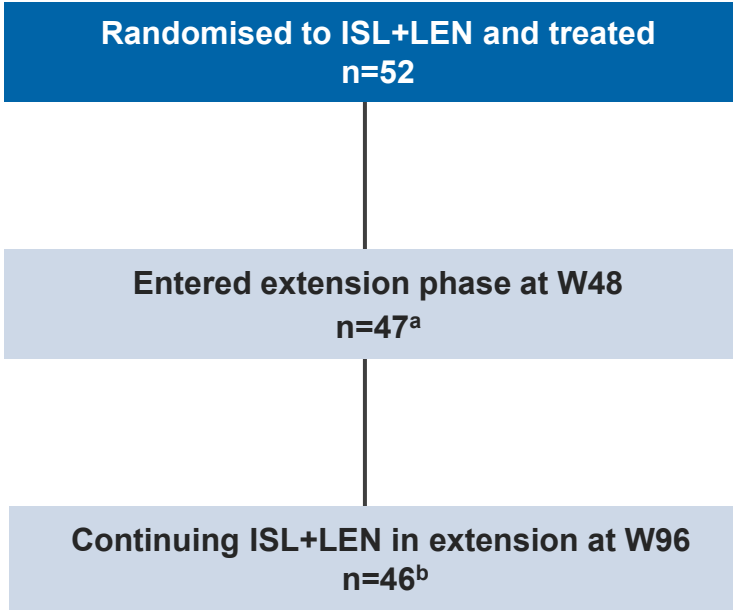
- Proportion with HIV-1 RNA ≥50 c/mL at Week 96
- Proportion with HIV-1 RNA <50 c/mL at Week 96
- Change from baseline in CD4+ T-cell count
- AEs

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; **QD**, daily; **QW**, weekly; **W**, Week.
1. Colson A, et al. CROI 2024; Abstract 208.

Participants



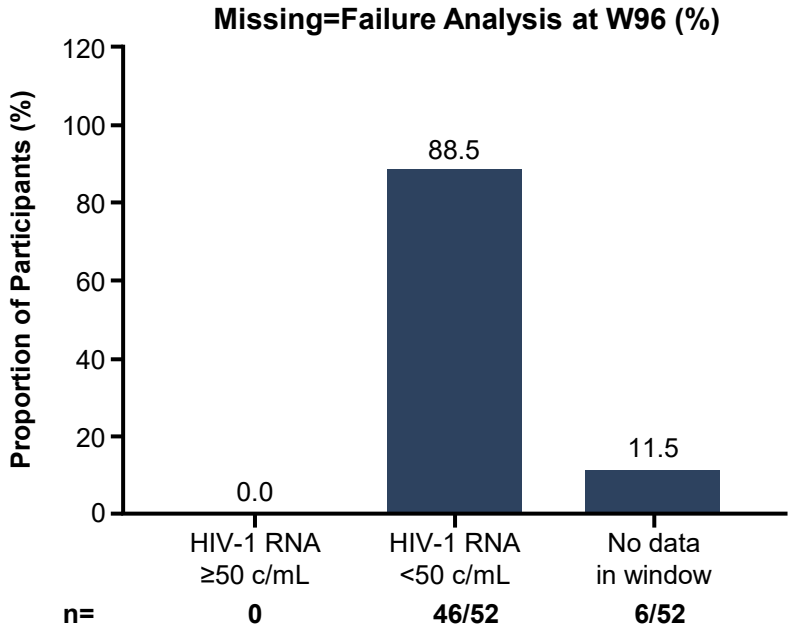
[a]Forty-seven out of 52 randomised and treated participants entered the extension phase. Participants who did not enter the extension phase (n=5): discontinued study due to unrelated AEs prior to W48 (n=2; large intestine perforation and renal colic in same participant [n=1]; and acute hepatitis B [n=1]), or discontinued study due to other reasons (n=3; participant decision [n=1] at W42, completed 48 weeks of randomised phase chose not to enter extension phase [n=2]). [b]Discontinued study (participant decision [n=1] at W60).
AE, adverse event; **ISL**, islatravir; **LEN**, Lenacapavir; **W**, week.

Baseline Demographic and Disease Characteristics

	ISL+LEN (n=52)
Median (range) age, years	40 (28–67)
Assigned female at birth, n (%)	10 (19.2)
Gender identity, n (%)	
Transgender female	1 (1.9)
Non-binary/third gender	0
Race, n (%)	
White	25 (48.1)
Black	21 (40.4)
Asian	2 (3.8)
American Indian or Alaska Native	1 (1.9)
Other	3 (5.8)
Hispanic or Latinx ethnicity, n (%)	13 (25.0)
Mean (95% CI) CD4+ T-cell count (cells/μL)	755 (692, 817)
Mean (95% CI) lymphocyte count x 10^3 cells/μL	1.94 (1.82, 2.07)
Median (IQR) body weight, kg	79.3 (70.4, 87.4)
Median (IQR) BMI, kg/m^2	26.9 (23.8, 30.0)

BMI, body mass index; **CI**, confidence interval; **IQR**, interquartile range; **ISL**, islatravir; **LEN**, lenacapavir.

Virologic Outcomes at Week 96



Participants with no data in window:

- Two participants discontinued due to unrelated AEs[a]
- Two participants discontinued due to personal reasons
- Two participants completed 48 weeks of the randomised phase and chose not to enter the extension phase due to personal reasons

All participants had HIV-1 RNA <50 c/mL at study discontinuation

- No participants had HIV-1 RNA ≥50 c/mL at W96 or at discontinuation; viral suppression was 100% in participants receiving ISL+LEN through W96
- No emergent resistance to ISL or LEN was detected
- Mean adherence was 99.3%[b]

[a]Two participants discontinued study due to unrelated AEs prior to W48 (large intestine perforation and renal colic in same participant [n=1]; acute hepatitis B [n=1]). [b]Adherence calculated by pill count.
AE, adverse event; **c/mL**, copies/mL; **ISL**, islatravir; **LEN**, Lenacapavir; **W**, week.

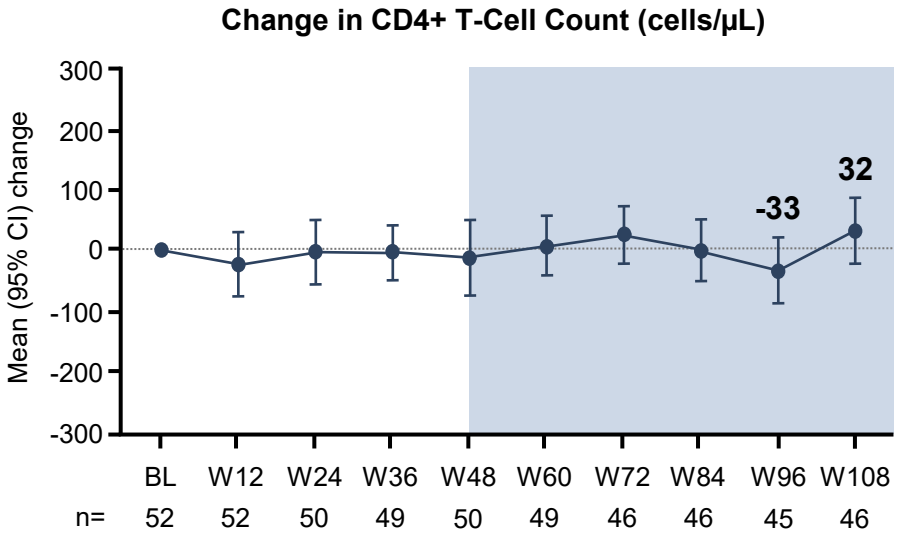
Adverse Events

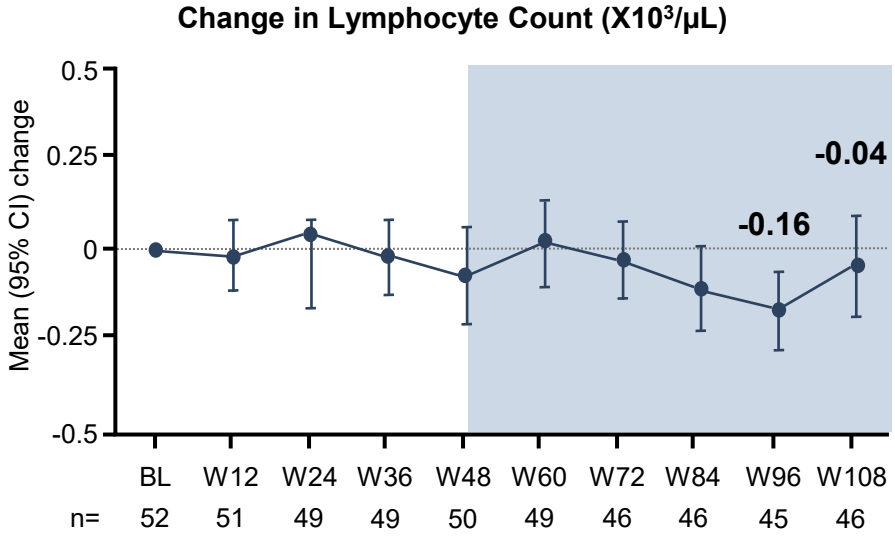
Participants, n (%)	ISL+LEN (n=52)
Any AE	46 (88.5)[a]
Treatment-related AEs	10 (19.2)
Grade 1 or 2	10 (19.2)
≥2 participants	
Dry mouth	2 (3.8)
Nausea	2 (3.8)
Grade 3 or higher	0
Serious AE	3 (5.8)[b]
Treatment-related	0
AE leading to study drug discontinuation	2 (3.8)[c]
Treatment-related	0

No Treatment-related Grade 3, Grade 4, or serious AEs[d]

[a]AEs occurring in >10%: diarrhoea (9) upper respiratory tract infection (8), arthralgia (6), COVID 19 (6); [b]Serious AEs: neurologic anesthesia complication (1), renal colic/colon perforation in same participant (1); pneumonia (n=1); [c]AEs leading to study discontinuation: acute HBV infection, renal colic/colon perforation in same participant; [d]Treatment-related adverse events were determined by the investigators.
AE, adverse event; **ISL**, islatravir; **LEN**, lenacapavir.

CD4+ T-cell and Lymphocyte Count Changes Through Week 96



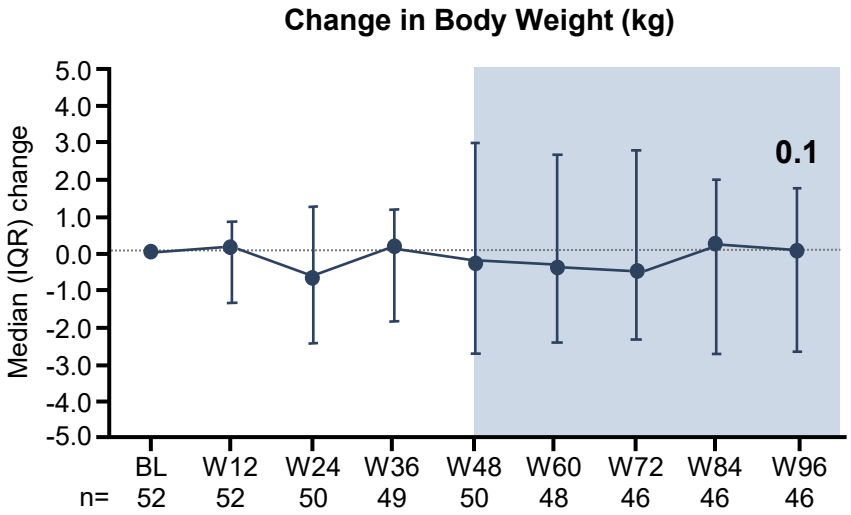


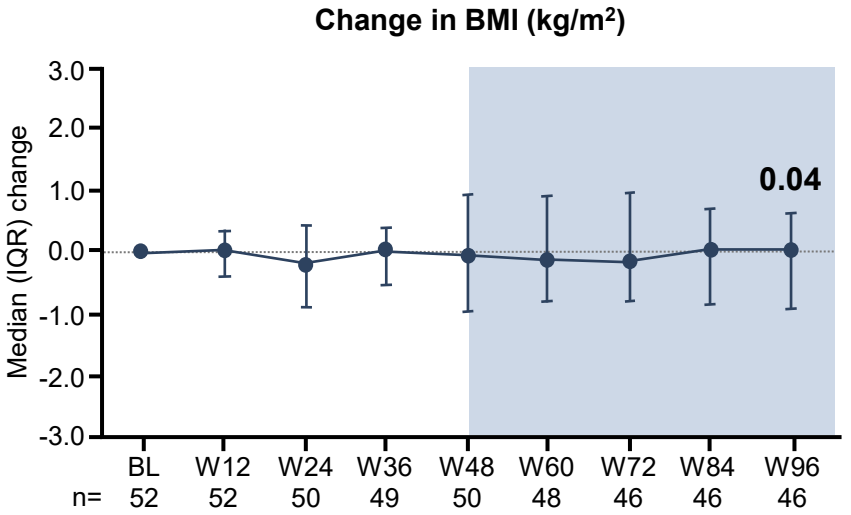
	Baseline	W96
Mean (95% CI) CD4+ T-cell count (cells/µL)	755 (692, 817)	708 (647, 770)
Mean (95% CI) lymphocyte count (x10³ cells/µL)	1.9 (1.8, 2.1)	1.8 (1.6, 1.9)

CD4⁺ T-cell and lymphocyte counts did not show clinically significant changes from baseline through W96, and no participants discontinued due to a decrease in either parameter

BL, baseline; **CI**, confidence interval; **W**, week.

Body Weight and BMI Changes Through Week 96





	Baseline	W96
Median (IQR) weight (kg)	79.3 (70.4, 87.4)	76.9 (70.7, 86.3)
Median (IQR) BMI (kg/m²)	26.9 (23.8, 30.0)	26.2 (24.0, 28.1)

Body weight and BMI remained similar to baseline through W96

BL, baseline; **BMI**, body mass index; **IQR**, interquartile range; **W**, week.

Conclusions

- Weekly oral ISL+LEN maintained virologic suppression through 96 weeks of treatment, and adherence remained high (99.3%)
  - No participant on ISL+LEN had HIV-1 RNA ≥50 c/mL at Week 96 or at study discontinuation
- Weekly oral ISL+LEN was well tolerated, with no treatment-related Grade ≥3 or serious AEs
- There were no clinically significant changes in $CD4^+$ T-cells or lymphocyte counts from baseline through Week 96
- Body weight and BMI remained stable from baseline through Week 96
- Two ongoing Phase 3 studies (ISLEND-1, NCT06630286; ISLEND-2, NCT06630299) are evaluating ISL+LEN FDC as a potential first, complete, once-weekly oral regimen for HIV-1 treatment

AE, adverse event; **BMI**, body mass index; **c/mL**, copies/mL; **ISL**, islatravir; **LEN**, lenacapavir; **FDC**, fixed-dose combination.

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