Once-Weekly Islatravir Plus Lenacapavir in Virologically Suppressed People with HIV: Week 48 Safety Profile, Efficacy, and Metabolic Changes

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Conclusions

- Weekly oral ISL+LEN maintained high rates of virologic suppression (94.2%) at Week 48 in people with HIV who were virologically suppressed
 - 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;

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 infection1
- Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor²
- Prior ISL studies have shown dose/exposure-related decreases in CD4+ T-cell and lymphocyte counts³
- Pharmacokinetic modelling indicates such declines are not expected with the 2 mg dose chosen for this study
- Lenacapavir (LEN) is a first-in-class capsid inhibitor⁵
- 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 group⁹ *LEN t₁₀=10-12 days; ISL-triphosphate t₁₀=7-9 days

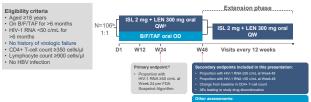
Objective

To investigate the efficacy and safety profile of QW oral ISL+LEN in people with HIV-1 who are virologically suppressed

Methods

Study Design

A Phase 2, Open-label, Active-Controlled Study in People with HIV who are Virologically Suppressed



0 mg of LEN was given on Day 1 and Day 2 for pharmacologic loading. ed, N=106; dosed, n=104. y mass index; c/mL, copies/ml; D, Day; FDA, Food and Drug Admin AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body ma HBV, hepatitis B virus; ISL, islatravir; LEN, lenacapavir; OD, daily; QW, weekly; W, Week.

Results

Baseline Demographic and Disease Characteristics

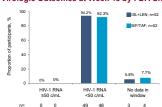
	ISL+LEN (n=52)	B/F/TAF (n=52)	Total (N=104)
Median (range) age, years	40 (28-67)	40 (26-76)	40 (26-76)
Assigned female at birth, n (%)	10 (19.2)	9 (17.3)	19 (18.3)
Gender identity, n (%)			
Transgender female	1 (1.9)	0	1 (1.0)
Non-binary/third gender	0	1 (1.9)	1 (1.0)
Race, n (%)			
White	25 (48.1)	27 (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 10³ 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)

References: 1. Clabom 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. CR01 2025; Abstract 192. 4. Vargo RC, et al. CR01 2025; Poster 4617. 5. Suderics Prescribing Information, available at https://www.gllead.com/-innedia/flee/pdb/imedicines/thiv/surinicne/aisnine/aisnines/thiv/surinicne/aisnines/

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Disclosures: AC, Gildead Sciences, inc. (consulting feese); Viii (honoraris), **GC**, Gilead Sciences, Inc. (grantfresearch support); Viiii (grantfresearch support); Abovie (grantfresearch support); PR, Gilead Sciences, Inc. (devisor/consultant, honoraris); Wild (advisor/consultant, grantfresearch support); Mansen (advisor/consultant, grantfresearch support); Mansen (advisor/consultant, grantfresearch support); Terratechnologies (advisor/consultant); Terratechnologies (advisor/consultant); Terratechnologies (advisor/consultant); Terratechnologies (advisor/consultant); Terratech

Results

Virologic Outcomes at Week 48 by FDA Snapshot Algorithm



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

ies/mL: FDA. Food and Drug Administration: ISL, islatravir; LEN, lenacapavi

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

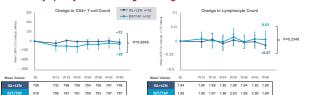
Laboratory Anomalies

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 hyperglycaemia	1/43 (2.3)	2/43 (4.7)
Glycosuria ^a	1/52 (1.9)	2/51 (3.9)
Hyperkalaemia	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

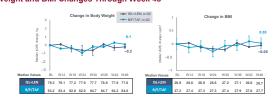
rred in participants with type 2 dia occurred after vigorous exercise in both participants.

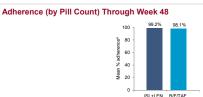
ALT, alanine transaminase; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; ISL, islatravir; LEN, lenacapavir.

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



Body Weight and BMI Changes Through Week 48





igh for ISL+LEN and B/F/TAF through Week 48