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

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Disclosures

Amy E. Colson: Gilead Sciences, Inc. (consulting fees); ViiV (honoraria); Merck (advisory board participation).

Gordon E. Crofoot: Gilead Sciences, Inc. (grant/research support); ViiV (grant/research support); Janssen Pharmaceuticals, Inc. (grant/research support); Merck (grant/research support); AbbVie (grant/research support).

Peter J. Ruane: Gilead Sciences, Inc. (advisor/consultant, honoraria); ViiV (advisor/consultant, honoraria).

Moti N. Ramgopal: Gilead Sciences, Inc. (advisor/consultant, honoraria, research support); ViiV (advisor/consultant, honoraria); AbbVie (honoraria).

Alexandra W. Dretler: Gilead Sciences, Inc. (grant/research support); ViiV (grant/research support, advisor/consultant); AbbVie (grant/research support).

Ronald G. Nahass: Gilead Sciences, Inc. (grants); Merck (grants); ViiV (grants); GSK (grants); Insmed (grants); IDSA (leadership or fiduciary role).

Gary I. Sinclair: Gilead Sciences, Inc. (advisor/consultant; grant/research support); Janssen (advisor/consultant; grant/research support; honoraria); ViiV (advisor/consultant; grant/research support; honoraria); Theratechnologies (advisor/consultant; grant/research support; honoraria); Merck (advisor/consultant; grant/research support; honoraria); AbbVie (grant/research support).

Mezgebe Berhe: none.

Afsoon Roberts: Gilead Sciences, Inc. (grant/research support).

Shauna Applin: Gilead Sciences, Inc. (grant or contracts; consultant funding; grant/research support; honoraria; advisory board participation; receipt of drugs through clinical trials).

Cynthia Brinson: Gilead Sciences, Inc. (funding; medical writing; advisor/consultant; honoraria); ViiV (advisor/consultant; honoraria); GSK (honoraria).

Fadi Shihadeh, **Shan-Yu Liu**, **Sharline Madera**, **Hadas Dvory-Sobol**, and **Devi SenGupta** are all employees and shareholders of Gilead Sciences, Inc.

Melissa A. Shaughnessy, **Cyril Llamoso**, and **Elizabeth G. Rhee** are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA; and shareholders of Merck & Co., Inc., Rahway, New Jersey, USA.

Joseph J. Eron: Gilead Sciences, Inc. (grant/contract payments made to his institution; consulting fees); ViiV (grant/contract payments made to his institution; consulting fees); Merck (consulting fees); AbbVie (consulting fees); Invivyd (fees, DSMB/advisory board); Taimed (fees, DSMB/advisory board).

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 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]

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

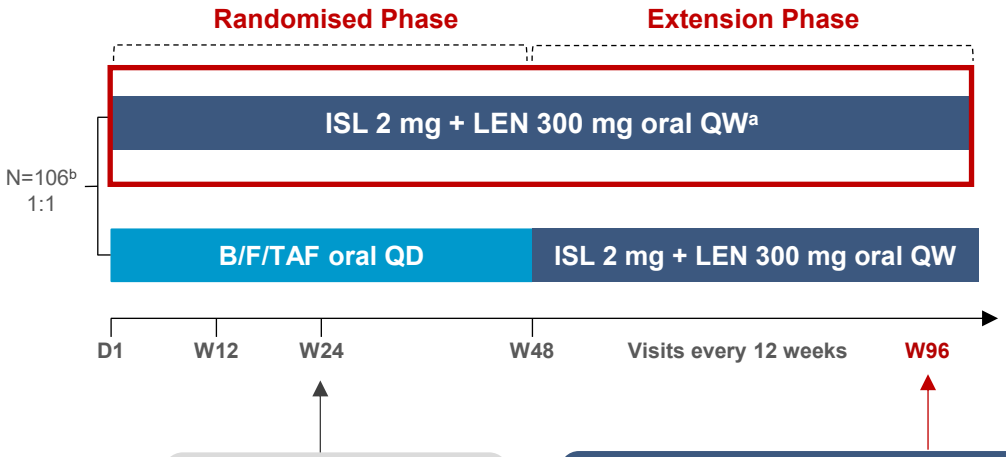
ARV, antiretroviral; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1.

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. 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. No participant on ISL+LEN had HIV-1 RNA ≥50 copies/mL at Week 48 or at study discontinuation

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

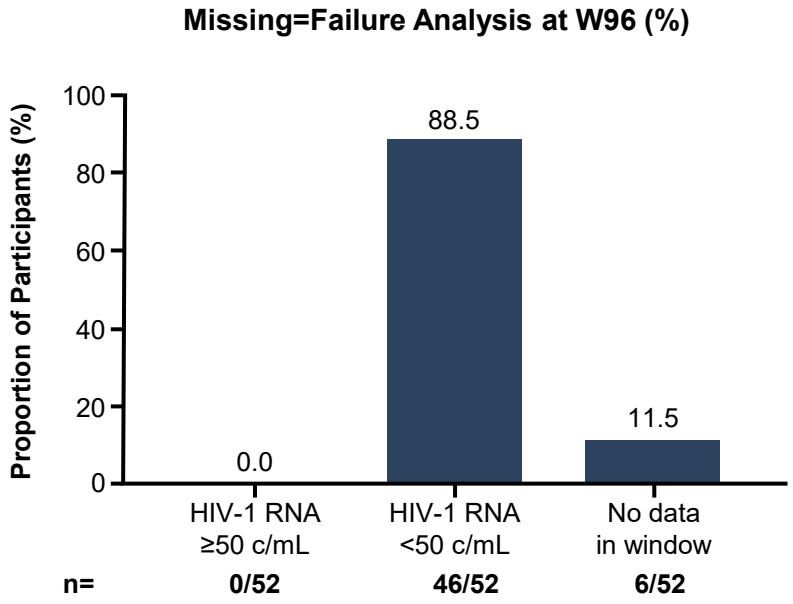
[a]600 mg of LEN was given on Day 1 and Day 2 for pharmacologic loading. [b]Randomised, N=106; dosed, n=104.
AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **BMI**, body mass index; **c/mL**, copies/ml; **D**, Day ; **FDA**, Food and Drug Administration; **HBV**, hepatitis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

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; **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 copies/mL at W96 or at discontinuation; at W96, all participants receiving ISL+LEN achieved viral suppression
- No emergent resistance to ISL or LEN was detected through W96
- 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.

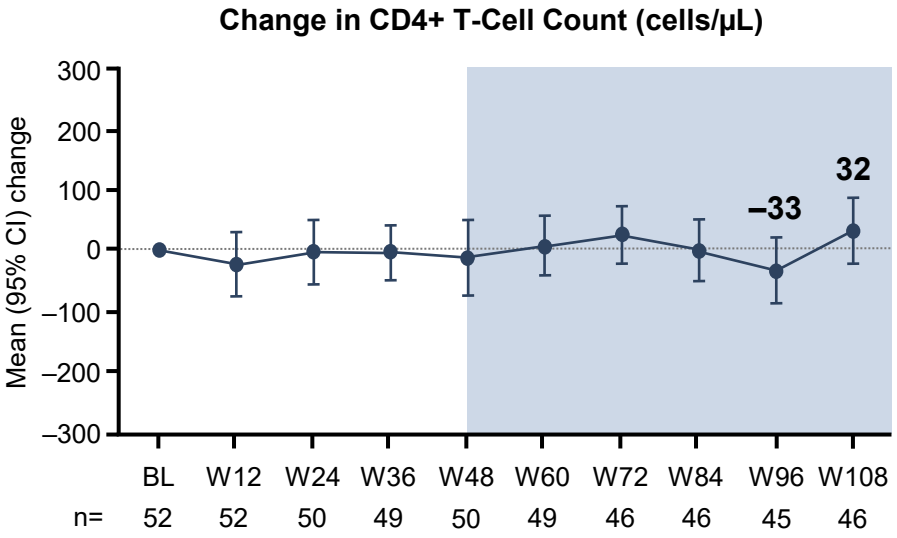
Adverse Events

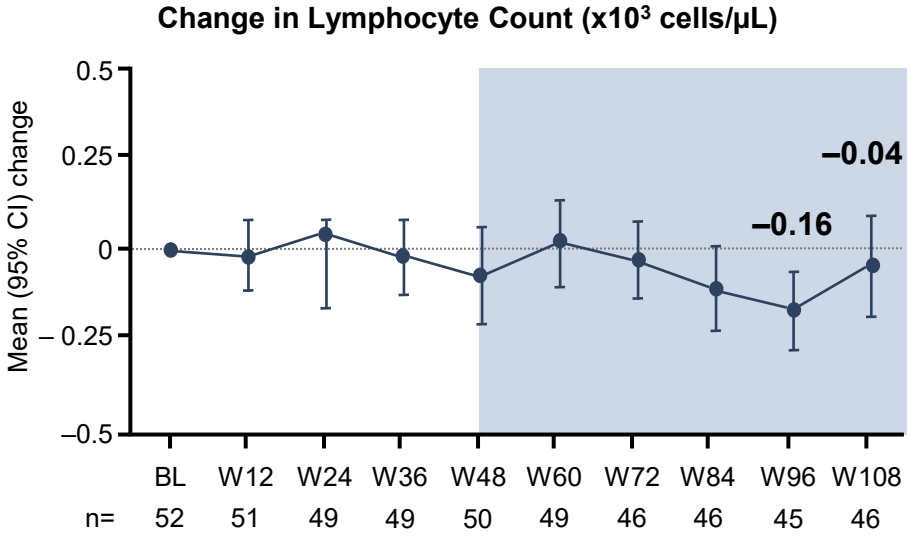
Participants, n (%)	ISL+LEN (n=52)
Any AE	46 (88.5)[a]
Treatment-related AEs	10 (19.2)
Grade 1 or 2	10 (19.2)
≥2 participants	
Dry mouth	2 (3.8)
Nausea	2 (3.8)
Grade 3 or higher	0
Serious AE	3 (5.8)[b]
Treatment-related	0
AE leading to study drug discontinuation	2 (3.8)[c]
Treatment-related	0

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

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

CD4+ T-cell and Lymphocyte Count Changes Through Week 108



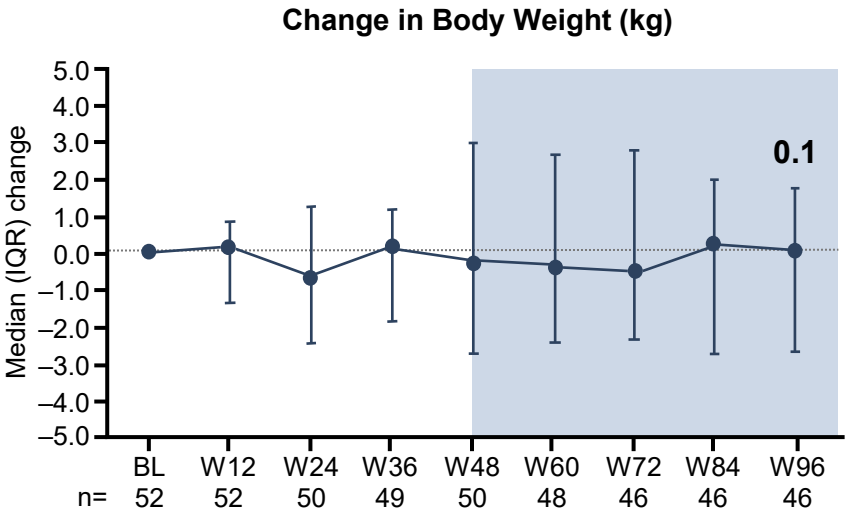


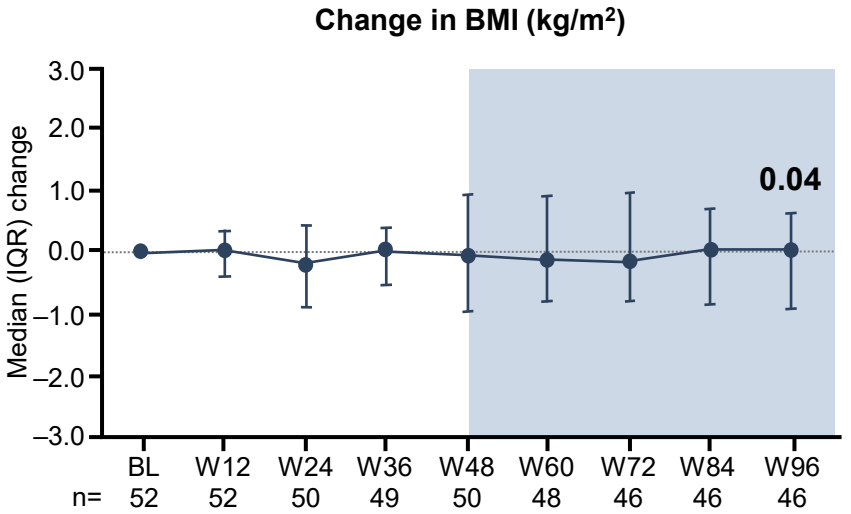
	Baseline	W96	W108
Mean (95% CI) CD4+ T-cell count (cells/µL)	755 (692; 817)	708 (647; 770)	762 (667; 858)
Mean (95% CI) lymphocyte count (x10³ cells/µL)	1.9 (1.8; 2.1)	1.8 (1.6; 1.9)	1.9 (1.7; 2.1)

CD4+ T-cell and lymphocyte counts did not show clinically significant changes from baseline through Week 108, and no participants discontinued due to a decrease in either parameter

BL, baseline; **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 stable through Week 96

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

Conclusions

- Weekly oral ISL+LEN maintained high rates of virologic suppression through 96 weeks of treatment and adherence remained high
  - 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 108
- 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 in PWH who are virologically suppressed

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

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

Acknowledgements

- We extend our thanks to the participants and their families
- We extend our thanks to all the participating investigators: Shauna Applin, Archana Asundi, Paul Benson, Mezgebe Berhe, Cynthia Brinson, Larry M. Bush, Amy E. Colson, Catherine M. Creticos, Gordon E. Crofoot, Edwin DeJesus, Alexandra W. Dretler, Joseph Eron, Cynthia Firnhaber, Edward Gardner, Linda Gorgos, Debbie Hagins, Shawn Hassler, Theo Hodge, Dushyantha Jayaweera, Ronald G. Nahass, Moti N. Ramgopal, Gary J. Richmond, Afsoon Roberts, Peter J. Ruane, Rachel Safran, Laura Salazar, William Sanchez, Patric Schine, Sorana Segal-Maurer, Peter Shalit, Cecilia M. Shikuma, Gary I. Sinclair, Christine Zurawski, Marcus Tellez, Kimberly Workowski
- This study was funded by Gilead Sciences Inc., Foster City, CA, USA and is part of a collaboration between Gilead Sciences Inc., Foster City, CA, USA and Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc, Rahway, NJ, USA
- All authors contributed to and approved the presentation; medical writing support was provided by Bill Wang, Ph.D. of Gilead Sciences, Inc, and was funded by Gilead Sciences, Inc.

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