Resistance Analysis of Weekly Islatravir Plus Lenacapavir in People With HIV at 48 Weeks

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Laurie A. VanderVeen[1]*, Silvia Chang[1], Lisa Selzer[1], Tracy L. Diamond[2], Ernest Asante-Appiah[2], Cyril Llamoso[2], Martin S. Rhee[1], Christian Callebaut[1]

[1]Gilead Sciences, Inc., Foster City, CA, USA; [2]Merck & Co., Inc., Rahway, NJ, USA

*Presenting author

Conclusions

- In virologically suppressed adults with HIV-1 treated with oral once-weekly (QW) islatravir (ISL) plus lenacapavir (LEN) for 48 weeks:
  - High rates of virologic suppression were maintained
  - One participant with pre-existing M184V/I also maintained virologic suppression
  - No participant developed treatment-emergent HIV-1 drug resistance
- These findings support the ongoing evaluation of ISL+LEN as an oral, QW treatment for HIV-1
  - Phase 3 studies evaluating the fixed-dose combination of QW oral ISL/LEN in virologically suppressed people with HIV-1 (PWH) are ongoing (ISLEND-1, NCT06630286; ISLEND-2, NCT06630299)[1,2]

Plain Language Summary

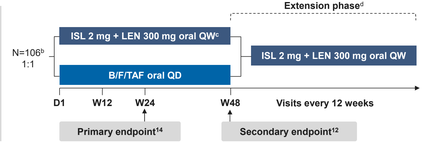
- Islatravir (a new medicine being studied for HIV-1 treatment) and lenacapavir (a medicine already approved as a twice-yearly injection for HIV-1 treatment) is a new combination of medicines that can be taken by mouth as a tablet once a week to treat HIV-1, unlike many other HIV-1 medicines that need to be taken every day
- An ongoing study is looking at how well islatravir plus lenacapavir work for HIV-1 treatment, and how safe it is. In this study, people with HIV-1 who were already taking the medication bictegravir/emtricitabine/tenofovir alafenamide for HIV-1 treatment either stayed on this treatment, or switched to islatravir plus lenacapavir
- Sometimes, the HIV-1 virus can develop resistance to medicines, which means that the medicines no longer work against the HIV-1 virus. We looked to see if participants with HIV-1 resistance that was present before the study affected how well islatravir plus lenacapavir worked, and if any new cases of resistance developed after people started islatravir plus lenacapavir
- We found that treatment with islatravir plus lenacapavir was effective in treating HIV-1, including in the few participants with HIV-1 resistance before starting the new treatments. In addition, no one developed resistance to islatravir plus lenacapavir during the study

Background

- Oral QW antiretrovirals have the potential to address pill fatigue and adherence challenges related to daily oral treatment for HIV-1 and reduce the injection burden associated with long-acting injectables[3]
- ISL is a nucleoside reverse transcriptase translocation inhibitor being investigated as an HIV-1 therapy[4]
- LEN is a first-in-class capsid inhibitor currently licensed as a twice-yearly subcutaneous injection for use in combination with other antiretrovirals in heavily treatment-experienced PWH[5]
- ISL and LEN both have novel mechanisms of action and additive inhibition of HIV-1, with non-overlapping resistance profiles and a higher barrier to the emergence of resistance when combined versus alone[6]
  - As capsid inhibitors are a new class of antiretrovirals, pre-existing resistance to LEN is unlikely[7,8]
- Both ISL and LEN have pharmacokinetic profiles suitable for oral QW dosing[9–11]
- NCT05052996 is an ongoing Phase 2 study evaluating the efficacy and safety of switching from oral once-daily bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) to oral QW ISL+LEN in virologically suppressed PWH **(Figure 1)**
  - Efficacy and safety data have been previously reported; oral QW ISL+LEN maintained a high rate (94.2%) of viral suppression at Week 48 **(Figure 2)**[12,13]

Figure 1. Study Design

Key eligibility criteria
- Aged ≥18 years
- On B/F/TAF for >6 months
- HIV-1 RNA <50 copies/mL for >6 months
- No history of virologic failure
- CD4+ T-cell count ≥350 cells/µL
- Lymphocyte count ≥900 cells/µL
- No HBV infection
- No NRTI or NNRTI resistance[a]



[a]The ongoing Phase 3 clinical trials do not have this resistance exclusion criteria.[1,2] [b]Randomized, N=106; dosed, n=104 (n=52 per group). [c]600 mg of LEN was given on D1 and D2 for pharmacologic loading. [d]Participants could elect to continue the study in post-W48 extension phase.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; D, Day; HBV, hepatitis B virus; ISL, islatravir; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; QD, once daily; QW, once weekly; W, Week.

Figure 2. Virologic Outcomes at Week 48 by FDA Snapshot Algorithm[12,13]

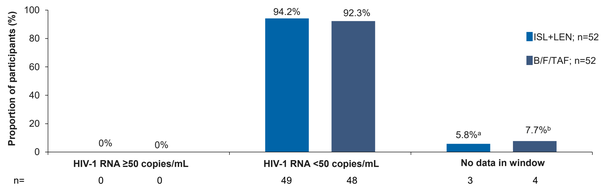


Figure adapted from Colson A, et al. IDWeek 2024.
[a]Two participants discontinued due to adverse events not related to study drug and one participant discontinued due to other reasons not related to study drug; all participants had HIV-1 RNA <50 copies/mL at study discontinuation. [b]Three participants discontinued due to other reasons not related to study drug and had HIV-1 RNA <50 copies/mL at study discontinuation; one participant had missing data during window but remained on study drug.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; FDA, Food and Drug Administration; ISL, islatravir; LEN, lenacapavir.

Objective

- To quantify and report interim data from an exploratory analysis of pre-existing HIV-1 resistance and post-baseline (on-treatment) resistance through Week 48 in the Phase 2 study

Methods

Pre-Treatment (Baseline) Analyses

- Protease (PR), reverse transcriptase (RT), and integrase (IN) genotyping was performed at screening (GenoSure Archive®, Monogram Biosciences), and historical HIV-1 genotype reports were collected if available
  - Nucleoside reverse transcriptase inhibitor (NRTI), non-NRTI (NNRTI), protease inhibitor (PI), and integrase strand transfer inhibitor (INSTI) resistance associated mutations (RAM) are presented in **Table 1**
- Absence of primary NRTI or NNRTI RAMs by historical or screening resistance genotype was required for study eligibility
- Participants who were eligible based on information available at the time of screening but found later to have pre-existing resistance after enrollment remained on study drug and were included in all analyses

Table 1. Primary RAMs for NRTI, NNRTI, PI, and INSTI Classes

Class	RAMs[a]
NRTI[b]	M41L, K65E/N/R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215F/Y, K219E/N/Q/R
NNRTI[b]	L100I, K101E/H/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C, M230I/L
PI	D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54L/M/V, Q58E, T74P, L76V, V82A/F/I/S/T, N83D, I84V, N88S, L90M
INSTI	T66A/I/K, E92G/Q/V, G118R, F121C/Y, G140R, Y143C/H/R, S147G, Q148H/K/R, N155H/S, R263K

[a]RAMs were based on the International Antiviral Society-USA list.[15] [b]These mutations were considered exclusionary for enrollment.
INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance associated mutation.

On-Treatment (Post-Baseline) Resistance Analyses

- Resistance testing was conducted for participants with HIV-1 RNA ≥200 copies/mL at the time of confirmed virologic failure (defined as two consecutive visits with HIV-1 RNA ≥50 copies/mL), or at study drug discontinuation/last visit
- Plasma HIV-1 RNA genotyping and phenotyping were conducted using the GeneSeq® Gag-Pro, PhenoSense® Gag-Pro, PhenoSense® GT, GeneSeq® Integrase, PhenoSense® Integrase assays (Monogram Biosciences)
- An alternative next-generation sequencing assay (Seq-IT GmbH & Co. KG, Kaiserslautern, Germany) was used in cases of assay failure

Single-Genome Sequencing

- Clonality of plasma HIV-1 RNA samples was evaluated by single-genome sequencing of the p6-RT (HXB2 nucleotides 1849–3410) region
  - RNA was extracted, reverse transcribed and cDNA subjected to nested polymerase chain reaction following endpoint dilution. Amplicons were sequenced using next-generation deep sequencing
  - Phylogenetic analysis of the sequences was performed by constructing a maximum likelihood tree (FastTree)

Results

Pre-Existing (Baseline) Resistance

- Pre-existing primary RAMs detected in the study population were uncommon, and similar between treatment arms **(Table 2)**
- Five participants who enrolled based on historical genotype data were subsequently found to have primary RAMs affecting NRTIs or NNRTIs on screening genotype:
  - ISL+LEN: M41M/L+M184M/V (n=1), V108V/I (n=1), L74L/V+K103K/N (n=1)
  - B/F/TAF: M184M/I (n=1), K219K/R (n=1)
- All participants in both the ISL+LEN and B/F/TAF groups with pre-existing NRTI or NNRTI resistance remained virologically suppressed at Week 48, including two participants with pre-existing M184V/I in RT (n=1 per group)

Table 2. Pre-Existing (Baseline) Primary Resistance to Four Main ARV Classes

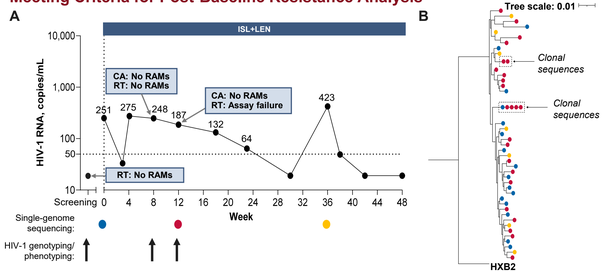
Pre-existing primary resistance substitutions, n/N (%)	ISL+LEN (n=52)	B/F/TAF (n=52)	All (N=104)
NRTI resistance	2/52 (3.8)	2/52 (3.8)	4/104 (3.8)
Any TAM[a]	1/52 (1.9)	1/52 (1.9)	2/104 (1.9)
M41L	1/52 (1.9)	0/52	1/104 (1.0)
L74V	1/52 (1.9)	0/52	1/104 (1.0)
M184V/I	1/52 (1.9)	1/52 (1.9)	2/104 (1.9)
K219R	0/52	1/52 (1.9)	1/104 (1.0)
NNRTI resistance	2/52 (3.8)	0/52	2/104 (1.9)
K103N	1/52 (1.9)	0/52	1/104 (1.0)
V108I	1/52 (1.9)	0/52	1/104 (1.0)
PI resistance	4/52 (7.7)	2/52 (3.8)	6/104 (5.8)
M46I/L	3/52 (5.8)	2/52 (3.8)	5/104 (4.8)
I84V	1/52 (1.9)	0/52	1/104 (1.0)
INSTI resistance	0/51	2/49 (4.1)	2/100 (2.0)
T66A	0/51	2/49 (4.1)	2/100 (2.0)

[a]TAMs are M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R in RT.
ARV, antiretroviral; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; ISL, islatravir; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RT, reverse transcriptase; TAM, thymidine analog mutation.

On-Treatment (Post-Baseline) Analysis

- One participant in the ISL+LEN group met criteria for post-baseline resistance analysis **(Figure 3)**
  - The participant had no pre-existing primary NRTI or NNRTI RAMs and was viremic at Day 1 (HIV-1 RNA 251 copies/mL)
  - The participant did not have treatment-emergent drug resistance and achieved sustained viral suppression after Week 36 while maintaining ISL+LEN **(Figure 3A)**
  - The participant demonstrated adequate plasma ISL and LEN levels
  - Single-genome analysis of longitudinal plasma sequences identified 15% (7/47) identical HIV-1 RNA sequences, suggesting clonal T-cell expansion may have contributed to low-level viremia **(Figure 3B)**

Figure 3. Virologic Analysis (A) and Phylogenetic Tree (B) of Participant Meeting Criteria for Post-Baseline Resistance Analysis



LEN RAMs are L56I, M66I, Q67H/K/N, K70H/N/S/R, N74D/S, A105S/T, T107A/C/N/S.
In Figure 3A, the horizontal dotted line denotes the HIV-1 RNA 50 copies/mL limit which defined virologic rebound in this study. Figure 3B shows the phylogenetic tree of plasma HIV-1 RNA single genome sequences, rooted to HXB2 consensus sequence. In Figure 3B, clonal sequences are indicated with dashed line boxes.
CA, capsid; ISL, islatravir; LEN, lenacapavir; RAM, resistance-associated mutation; RT, reverse transcriptase.

References: 1. ClinicalTrials.gov. Study to Compare an Oral Weekly Islatravir/Lenacapavir Regimen With Bictegravir/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed People With HIV-1 (ISLEND-1). Available at: https://clinicaltrials.gov/study/NCT06630286. Accessed Jan 2025. **2.** ClinicalTrials.gov. Study to Compare an Oral Weekly Islatravir/Lenacapavir Regimen With Standard of Care in Virologically Suppressed People With HIV-1 (ISLEND-2). Available at: https://clinicaltrials.gov/study/NCT06630299. Accessed Jan 2025. **3.** Claborn KR, et al. *Psychol Health Med.* 2015;20:255–65. **4.** Schürmann D, et al. *Lancet HIV.* 2020;7:e164–72. **5.** Sunlenca® Prescribing Information. Available at: https://www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.pdf. Accessed Jan 2025. **6.** Diamond T, et al. *Antimicrob Agents Chemother.* 2024;68:e0033424. **7.** Marcelin A-G, et al. *J Antimicrob Chemother.* 2020;75:1588–90. **8.** Yant SR, et al. IAS 2019; Abstract TUPE075. **9.** Zhang H, et al. CROI 2022; Poster 433. **10.** Shaik N, et al. AIDS 2022; Poster PESUB23. **11.** Matthews R, et al. *Clin Trans Sci.* 2021;14:1935–44. **12.** Colson A, et al. IDWeek 2024; Presentation 577. **13.** Colson A, et al. HIV Drug Therapy Glasgow 2024; Presentation O21. **14.** Colson A, et al. CROI 2024; Oral 14. **15.** Wensing AM, et al. *Top Antivir Med.* 2022;30:559–74.

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Conflicts of Interest:
TLD, EA-A, and **CL** are all employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and shareholders of Merck & Co., Inc., Rahway, NJ, USA.
LAV, SC, LS, MSR, and **CC** are all employees and shareholders of Gilead Sciences, Inc.