Evaluation of Relative Bioavailability and Food Effect of a Fixed-Dose Combination Tablet of Islatravir and Lenacapavir

P-359

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Conclusions

- The pharmacokinetic (PK) and safety results from this relative bioavailability and food-effect characterization of an islatravir/lenacapavir (ISL/LEN) 2/300 mg fixed-dose combination (FDC) tablet support continued clinical development in Phase 3 trials of an ISL/LEN once-weekly (QW) oral FDC dosing regimen, without regard to food, for the treatment of HIV-1 infection
- ISL and LEN exposures (area under the time-concentration curve extrapolated to infinity [AUC_{inf}] and maximum concentration [C_{max}]) were generally similar for ISL/LEN FDC vs single-agent co-administration, except for the slightly lower ISL C_{max} for the FDC, which is not considered clinically meaningful
- ISL exposures were similar, while LEN exposures were higher with fed versus fasted administration of the ISL/LEN FDC. The increase in LEN exposure in the fed state is not considered clinically relevant and is in alignment with the previously observed food effect for LEN as a single agent[1]
- ISL and LEN had a favorable safety profile and were generally well tolerated
- The efficacy and safety of the ISL/LEN FDC is currently being evaluated in the ongoing Phase 3 trials ISLEND-1 (NCT06630286)[2] and ISLEND-2 (NCT06630299)[3]

Plain Language Summary

- Islatravir is a medicine being studied as one part of a multi-medicine treatment for HIV along with another medicine called lenacapavir
- Sometimes, when medicines are given together, they can affect how well each medicine gets into a person's blood, which can change how much medicine is available to do its job
  - Taking a medication with food instead of taking it on an empty stomach can affect how much medication is able to get into the blood and do its job
- We did a study to see if islatravir and lenacapavir taken as two different pills would get the same amount of medicine into the blood as if they were taken combined into one tablet
  - The study also looked at whether taking the combined tablet with food would change the amount of medicine in the blood versus taking the tablet on an empty stomach
- This study found that people taking islatravir and lenacapavir in a combined tablet had similar levels of medicine as the people who took each medicine as two separate pills
  - It did not matter if the tablet was taken with food or on an empty stomach
  - Islatravir and lenacapavir were did not cause severe side effects in each situation as well
- These results show that islatravir and lenacapavir can be given as a combined tablet with or without food

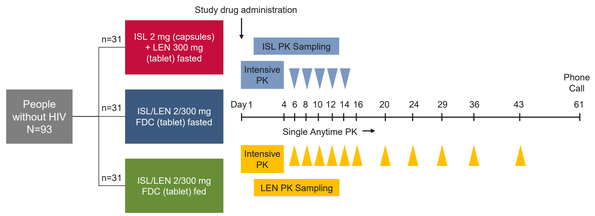
Introduction

- A combination treatment consisting of ISL, a nucleoside reverse transcriptase translocation inhibitor, and LEN, an HIV-1 capsid inhibitor, has the potential to provide a complete, QW oral regimen for HIV-1 treatment[4-6]
- In an ongoing Phase 2 study (NCT05052996) of virologically suppressed people with HIV-1, 94% of participants switching to QW co-administration of single-agent ISL capsules and LEN tablets maintained virologic suppression at Week 48[7]
- Here, we evaluated the relative bioavailability of ISL/LEN FDC vs ISL and LEN single-agent co-administration, and the effect of food on ISL/LEN FDC PK in a Phase 1 study, to inform development of the FDC for Phase 3 studies
- Two ongoing Phase 3 studies, ISLEND-1 (NCT06630286)[2] and ISLEND-2 (NCT06630299)[3], are evaluating an ISL/LEN 2/300 mg FDC tablet in adults with HIV-1 who are virologically suppressed on either bictegravir/emtricitabine/tenofovir alafenamide or another standard-of-care regimen

Methods

- In this Phase 1, open-label, parallel-design study, participants without HIV-1 received single oral doses of single-agent ISL 2 mg (2 x 1 mg capsules) and LEN 300 mg (1x tablet) simultaneously under fasted conditions (n=31) or an ISL/LEN FDC 2/300 mg tablet under fasted (n=31) or fed (high-fat; ~50% calories from fat) conditions (n=31) (**Figure 1**)
- Participants were aged 18–55 years, with body mass index ≥19.0–≤30.0 kg/m^2 at screening, and with no clinically significant abnormalities from laboratory evaluations or 12-lead electrocardiogram evaluations as assessed by the investigator
  - Participants refrained from use of prescription and over-the-counter medicines during the study

Figure 1. Study Design



Safety was assessed at each visit and adverse events were recorded through the Day 61 follow-up phone call. PK sampling occurred through Day 14 for ISL and Day 43 for LEN. FDC, fixed-dose combination; ISL, islatravir; LEN, lenacapavir; PK, pharmacokinetics.

- Plasma PK samples were analyzed using validated liquid chromatography coupled with tandem mass spectrometry methods
- PK parameters were determined by standard non-compartmental analysis; geometric least-squares mean ratios were calculated for test vs reference treatment
  - An analysis of variance model with cohort as a fixed effect was fitted to the natural logarithmic transformation of PK parameters for each analyte with two-sided 90% CI
- Safety was monitored by physical examinations, clinical laboratory tests, and adverse event reporting

Results and Discussion

Disposition and Baseline Characteristics

- Overall, 93 participants were enrolled, with 31 per cohort
  - Baseline characteristics were similar across cohorts (**Table 1**)
  - The overall median age was 35 years, and 55% of participants were female
- All enrolled participants completed study drug dosing, and 91 participants (97.8%) completed the study
  - Two participants (2.2%) prematurely discontinued study (both in the ISL/LEN FDC group); n=1 lost to follow-up and n=1 withdrawal of consent

Table 1. Baseline Characteristics

Characteristic	ISL + LEN fasted (n=31)	ISL/LEN FDC fasted (n=31)	ISL/LEN FDC fed (n=31)
Median age (range), years	35 (20–54)	33 (18–55)	37 (19–54)
Female sex at birth, n (%)	18 (58.1)	15 (48.4)	18 (58.1)
Race, n (%)			
American Indian or Alaska Native	0	2 (6.5)	1 (3.2)
Asian	0	0	1 (3.2)
Black or African American	3 (9.7)	6 (19.4)	2 (6.5)
White	28 (90.3)	22 (71.0)	27 (87.1)
Other	0	1 (3.2)	0
Hispanic or Latine ethnicity, n (%)	3 (9.7)	4 (12.9)	2 (6.5)
Mean BMI (SD), kg/m^2	26.0 (2.7)	26.4 (3.2)	26.5 (2.5)
Mean weight (SD), kg	77.3 (11.8)	77.7 (13.3)	77.9 (12.6)

BMI, body mass index; FDC, fixed-dose combination; ISL, islatravir; LEN, Lenacapavir; SD, standard deviation.

FDC vs Single-Agent Co-Administration

- AUC_{inf} were generally similar, with ISL % geometric least squares mean (GLSM) ratios (90% CI) of 107 (97.8; 116) and LEN %GLSM ratios (90% CI) of 90.2 (72.1; 113) for ISL/LEN FDC vs single-agent co-administration under fasted conditions (**Table 2; Figure 2**)
- There was a lower ISL mean C_{max} for the FDC (11.0 ng/mL) than with co-administration (16.5 ng/mL)
  - The lower C_{max} did not lead to an overall decrease in exposure, as the AUC_{inf} between the two cohorts was similar, indicating slower absorption for the FDC
  - This finding is not unexpected, as the apparent slower rate of absorption for ISL from the FDC is likely due to a relatively slower initial release from the FDC tablet, considering the formulation and size difference between the ISL capsule and the FDC tablet

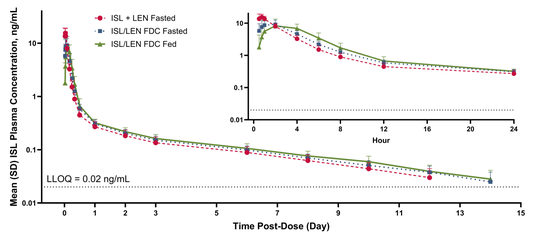
Table 2. PK Parameter Estimates and Comparisons

	PK parameter	ISL and LEN co-administration, fasted (n=31)	ISL/LEN FDC, fasted (n=31)	ISL/LEN FDC, fed (n=31)	%GLSM ratio (90% CI)	
					Relative bioavailability (ISL/LEN FDC vs ISL and LEN co-administration, fasted)	Food effect (ISL/LEN FDC fed vs fasted)
ISL	C_{max}, ng/mL	16.5 (22.0)	11.0 (35.0)	11.7 (37.7)	64.4 (56.7–73.1)	106 (90.6–123)
	AUC_{inf}, h•ng/mL	72.6 (22.3)	76.7 (17.1)[a]	82.0 (17.0)	107 (97.8–116)	107 (99.4–115)
	T_{max}, h	0.750 (0.500–0.750)	1.03 (0.750–2.00)	2.00 (2.00–4.00)	-	-
	$t_{1/2}$, h	95.4 (87.5–103)	101 (94.4–110)[a]	103 (94.7–114)	-	-
LEN	C_{max}, ng/mL	18.1 (61.3)	19.4 (64.9)	28.6 (75.1)	103 (80.6–132)	143 (108–189)
	AUC_{inf}, h•ng/mL	6290 (50.4)	6020 (66.1)[a]	7740 (69.0)	90.2 (72.1–113)	127 (97.7–164)
	T_{max}, h	4.00 (4.00–24.0)	4.00 (4.00–4.00)	4.00 (4.00–6.00)	-	-
	$t_{1/2}$, h	279 (239–306)	317 (246–371)[a]	304 (246–345)	-	-

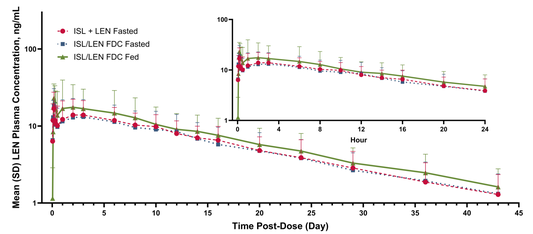
PK parameters are presented as mean (% coefficient of variation) except T_{max} and $t_{1/2}$ which are presented as median (interquartile range). [a]n=30 due to early discontinuation after Day 3 in one participant. AUC_{inf}, area under the curve extrapolated to infinite time; C_{max}, maximum concentration; FDC, fixed-dose combination; GLSM, geometric least-squares mean; h, hours; ISL, islatravir; LEN, lenacapavir; PK, pharmacokinetics; T_{max}, time to C_{max}; $t_{1/2}$, half-life.

Figure 2. Arithmetic Mean (SD) Plasma Concentration-Time Profiles of (A) ISL and (B) LEN After a Single Dose of ISL and LEN Single-Agent Co-Administration Under Fasted Conditions, and ISL/LEN FDC Under Fasted or Fed Conditions[a]

A) ISL Concentrations



B) LEN Concentrations



[a]First 24 hours shown in insets. The LLOQ for ISL and LEN was 0.02 ng/mL and 0.1 ng/mL, respectively.
FDC, fixed-dose combination; ISL, islatravir; LEN, lenacapavir; LLOQ, lower limit of quantitation.

Food Effect

- ISL exposures (AUC_{inf} and C_{max}) were similar with fed versus fasted administration of a single dose of ISL/LEN 2/300 mg FDC (**Figure 2A, Table 2**)
- LEN exposures were higher (27% and 43% higher AUC_{inf} and C_{max}, respectively) with fed versus fasted administration of a single dose of ISL/LEN 2/300 mg FDC (**Figure 2B, Table 2**)
  - The observed higher LEN exposure under the fed state is not considered clinically relevant and is in alignment with previously observed food effect for LEN administered as a single agent[7]

Safety

- ISL and LEN were generally well tolerated when administered individually or as an FDC in the fed or fasted state

References: **1.** Singh R, et al. *Clin Pharmacol in Drug Dev.* 2025;14:324–32. **2.** https://clinicaltrials.gov/study/NCT06630286. Accessed October 7, 2025. **3.** https://clinicaltrials.gov/study/NCT06630299. Accessed October 7, 2025. **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; Presentation 577.

Acknowledgments: We extend our thanks to the participants, their families, and all investigators and staff. 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. Medical writing and editorial support were provided by Luke Ward and Sherriden Beard of Ashfield MedComms (Macclesfield, UK), an Inizio company, and was funded by Gilead Sciences, Inc.

Disclosures: **Jing Niu, Haeyoung Zhang, John Ling, Sharline Madera, Nerissa Kwok, Steve West,** and **Dhananjay Marathe** are all employees and shareholders of **Gilead Sciences, Inc**. **Diane Longo, Gillian Gillespie, Cyril Llamoso** 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.**

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