Evaluation of Potential Drug-Drug Interactions Between Islatravir and Lenacapavir

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Introduction

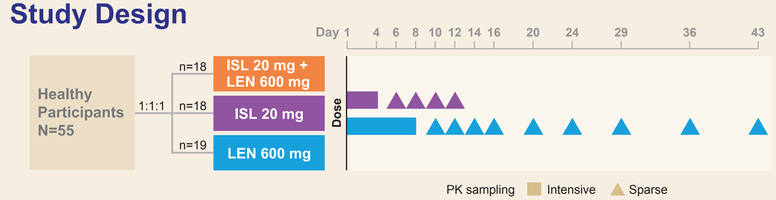
- Coadministration of islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor, and lenacapavir (LEN), a capsid inhibitor, has the potential to offer a safe and efficacious oral once-weekly regimen for the treatment of HIV-1 infection[1,2]
- ISL, which is not a substrate of cytochrome P450 (CYP) enzymes, is primarily metabolized via adenosine deaminase, with substantial elimination via urinary excretion; ISL also has no effect on CYP enzymes or major transporters[3]
- LEN is a substrate of CYP3A, uridine diphosphate-glucuronosyl transferase 1A1, and P-glycoprotein transporter, and a moderate inhibitor of CYP3A[4]
- Available data indicate that significant systemic drug-drug interactions (DDIs) between ISL and LEN are unlikely
- The present clinical study examined potential DDIs between ISL and LEN following oral coadministration

Objectives

- To evaluate the pharmacokinetics (PK), safety, and tolerability of a single dose of oral ISL and oral LEN administered alone or in combination

Methods

Study Design



- A Phase 1, open-label, parallel-design, single-dose, 3-cohort study was conducted in 55 healthy participants who received single oral doses of coadministered ISL 20 mg and LEN 600 mg (test: n=18), ISL 20 mg only (reference: n=18), or LEN 600 mg only (reference: n=19)
- 15 evaluable participants/cohort with 20% overage were enrolled for ≥90% power with no-effect boundaries of 60–167%, assuming a coefficient of variation (CV) of 41.4%, based on ISL area under the curve (AUC) from a previous study[1]
- Plasma PK samples were collected up to Day 12 for ISL and to Day 43 for LEN, and were analyzed with high-performance liquid chromatography–tandem mass spectrometry using validated methods
- DDI assessment was performed using geometric least-squares mean (GLSM) ratios and 90% confidence intervals (CIs) of test vs reference treatments for PK parameters AUC from time 0 to ∞ (AUC_∞) and maximum concentration (C_{max})
- Safety was monitored by vital signs, physical examinations, electrocardiograms, and clinical laboratory tests

Results

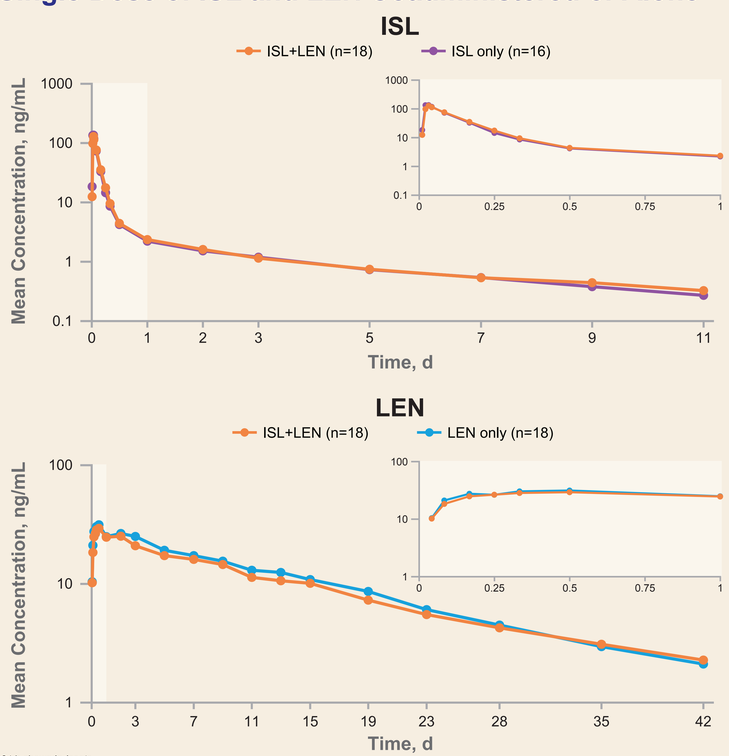
Baseline Characteristics*

	ISL+LEN (n=18)	ISL Only (n=18)	LEN Only (n=19)
Sex at birth, n			
Male	14	11	13
Female	4	7	6
Mean age, y (SD)	32 (6.4)	32 (7.7)	35 (5.1)
Mean BMI, kg/m² (SD)	25.5 (2.71)	25.9 (3.61)	24.8 (3.19)
Race, n			
Asian	2	4	3
Black or African-American	3	4	8
Native Hawaiian or other Pacific Islander	1	0	0
White	12	10	8

*PK analysis was performed for 16 participants in ISL-only cohort and for 18 in LEN-only cohort due to important protocol deviations. BMI, body mass index; SD, standard deviation.

- Participant characteristics were comparable for sex at birth, age, BMI, and race between cohorts

Arithmetic Mean Plasma Concentration-Time Profiles After a Single Dose of ISL and LEN Coadministered or Alone*



*Initial 24 h shown in *insets*.

PK Parameter Estimates and Comparisons*

	Mean PK Parameter (%CV)	ISL+LEN (n=18)	Reference: ISL Only (n=16) or LEN Only (n=18)	ISL+LEN vs Reference %GLSM Ratio (90% CI)
ISL	C_{max}, ng/mL	145 (41.3)	165 (42.2)	87.9 (68.7, 113)
	AUC_∞, h·ng/mL	674 (25.4)	642 (25.8)	105 (90.2, 123)
	T_{max}, h†	0.75 (0.50, 2.00)	0.75 (0.50, 2.00)	ND
	Apparent terminal $t_{1/2}$, h	121 (18.7)	99.1 (14.6)	ND
LEN	C_{max}, ng/mL	33.7 (77.7)	37.9 (57.0)	80.1 (50.9, 126)
	AUC_∞, h·ng/mL	9840 (51.0)	10,800 (56.9)	88.6 (60.5, 130)
	T_{max}, h†	8.00 (1.00, 48.0)	10.0 (2.00, 312)	ND
	Apparent terminal $t_{1/2}$, h	296 (23.5)	308 (24.7)	ND

*Data are shown to 3 significant digits; results based on nominal time; †Median (minimum, maximum). ND, not determined; T_{max}, time to C_{max}; $t_{1/2}$, half-life.

- PK results based on nominal times for %GLSM ratios of PK parameters AUC_∞ and C_{max} for ISL were 105% and 87.9%, respectively, and for LEN were 88.6% and 80.1%, respectively
- Higher %CV was observed for LEN vs ISL, resulting in a wider 90% CI
- Point estimates of %GLSM ratios and 90% CIs show that PK of ISL and LEN were similar when administered alone or in combination

Safety

- Coadministration of ISL and LEN was generally well tolerated
- No serious, or Grade 3 or 4 adverse events occurred
- No clinically relevant Grade 3 or 4 laboratory abnormalities occurred

Conclusions

- PK data showed no significant DDIs for oral coadministration of ISL and LEN
- Data from this study support the clinical development of ISL and LEN as a combination therapy for treatment of HIV-1 infection

References: 1. Dvory-Sobol H, et al. Curr Opin HIV AIDS 2022;17:15-21; 2. Schürmann D, et al. Lancet HIV 2020;7:e164-72; 3. Bleasby K, et al. Viruses 2021;13:1566; 4. Begley R, et al. CROI 2021, abstr 89, Oral-02.

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