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Pharmacokinetics of oral islatravir plus lenacapavir given once weekly in an open-label, active-controlled, phase 2 study of virologically suppressed people living with HIV-1

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Background

- Once-weekly (QW) antiretrovirals provide an opportunity to address challenges associated with daily oral treatment for HIV-1 such as pill fatigue, stigma and suboptimal adherence[1,2]
- Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor being developed for the treatment of HIV-1[3,4]
  - ISL is phosphorylated intracellularly to its pharmacologically active triphosphate (TP) form (ISL-TP)[4]
- Lenacapavir (LEN) is a first-in-class HIV-1 capsid inhibitor that interferes with multiple stages of the HIV life cycle[5]
- QW oral ISL+LEN combines agents with novel mechanisms of action, potent antiviral activity, additive inhibition of HIV-1, and pharmacokinetic (PK) profiles that support long-acting QW dosing[5,6]
- Oral ISL+LEN QW is being evaluated as switch therapy in a phase 2 study of adults living with HIV-1 who were virologically suppressed while receiving once-daily oral bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF)
  - Oral ISL+LEN QW maintained high rates of virologic suppression (94.2%) and was generally well tolerated through Week 48[7]
  - There were no between-group differences in CD4+ T-cell or lymphocyte count changes from baseline to Week 48 and no participants discontinued due to a decrease in CD4+ T-cell or lymphocyte counts[7]

Objective

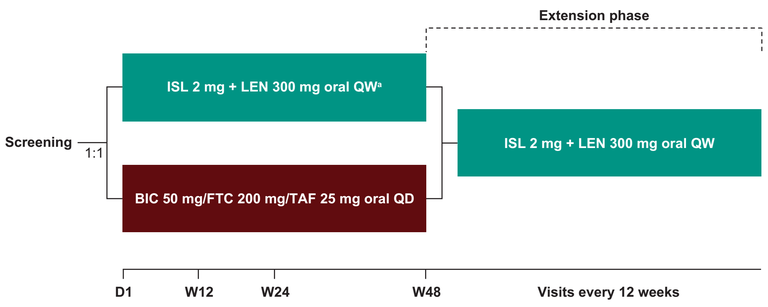
- To evaluate the PK of oral ISL+LEN QW through Week 24 in virologically suppressed people living with HIV-1

Methods

Study design

- This was a randomized, open-label, multicenter, active-controlled, phase 2 study in virologically suppressed people living with HIV-1 (MK-8591D-045; GS-US-563-6041; NCT05052996; **Figure 1**)
  - Key inclusion criteria at screening were age ≥18 years, treatment with BIC/FTC/TAF for ≥24 weeks, plasma HIV-1 RNA <50 copies/mL, and CD4+ T cells ≥350 cells/mm^3
- Eligible participants (N = 106) were randomized (1:1) to switch to ISL 2 mg plus LEN 300 mg QW or to continue oral BIC 50 mg/FTC 200 mg/TAF 25 mg once-daily for 48 weeks

Figure 1. Study design



BIC, bictegravir; D, day; FTC, emtricitabine; ISL, islatravir; LEN, lenacapavir; QD, once daily; QW, once weekly; TAF, tenofovir alafenamide; W, week.

[a]A loading dose of LEN 600 mg was given on Days 1 and 2.

The randomized treatment period is at least 48 weeks. At the Week 48 visit, all participants will be given the option to take ISL+LEN in an extension phase until the drug is commercially available or until Gilead elects to discontinue the development of ISL+LEN, whichever occurs first.

ISL and LEN PK sampling and analysis

- Sparse PK samples were collected from all participants on Day 1 (approximately 1 hour post-dose) and at any time on Weeks 4, 8, 12, 18, and 24
- An intensive PK substudy was conducted in 14 participants in the ISL+LEN arm, with sample collection for plasma ISL and LEN on Day 1, Day 2 (LEN only), and Week 12 (ISL and LEN)
  - Plasma concentrations of ISL and LEN were summarized by nominal sampling time
  - PK parameters were summarized using descriptive statistics

ISL population PK analysis

- A population PK (popPK) model developed from phase 1-3 studies of ISL was used to predict ISL-TP exposure from plasma ISL concentrations
- PK/pharmacodynamics (PD) models developed from phase 2 and 3 studies of ISL were used to simulate CD4+ T-cell and lymphocyte counts using popPK-predicted ISL-TP exposures

Results

Study population

- 104 participants were randomized and received ≥1 dose of study drug: 52 were assigned to receive ISL+LEN and 52 to receive BIC/FTC/TAF (**Table 1**)
  - As of Week 48, 6 participants (5.8%) had discontinued the study drugs prematurely (ISL+LEN: 3 [5.8%]; BIC/FTC/TAF: 3 [5.8%])

Table 1. Baseline demographics and characteristics

	ISL+LEN QW n = 52	BIC/FTC/TAF QD n = 52	Total N = 104
Age, median (range), 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)
Nonbinary/third gender	0	1 (1.9)	1 (1.0)
Race, n (%)			
White	25 (48.1)	27 (51.9)	52 (50.0)
Black/African American	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	1 (1.9)	1 (1.0)
Other	3 (5.8)	5 (9.6)	8 (7.7)
Ethnicity, n (%)			
Hispanic or Latinx	13 (25.0)	17 (32.7)	30 (28.8)
CD4, mean (SD), cells/μL	755 (223.6)	818 (271.3)	786 (249.5)
Total lymphocytes, mean (SD), × 10^3 cells/μL	1.94 (0.445)	1.95 (0.652)	1.94 (0.556)

BIC, bictegravir; FTC, emtricitabine; ISL, islatravir; LEN, lenacapavir; SD, standard deviation; TAF, tenofovir alafenamide; QD, once daily; QW, once weekly.

Pharmacokinetics

- Observed plasma concentrations for ISL and LEN across the dosing intervals were in line with expected ranges between trough and maximum concentrations (C_{trough} and C_{max}) for both analytes (**Table 2**)
- At steady state, ISL and LEN exposures (area under the concentration-time curve from time 0 to 8 hours [$AUC_{0\text{-}8h}$], C_{max}, concentration 8 hours after dosing [C_{8h}]) showed 2.1- to 2.6-fold accumulation for LEN and no accumulation for ISL, compared with Day 1 (**Table 2**)

Table 2. Plasma pharmacokinetic parameters of ISL and LEN (intensive PK substudy)

PK parameter		Day 1 ISL 2 mg + LEN 600 mg n = 13	Day 2 LEN 600 mg n = 13	Steady state ISL 2 mg + LEN 300 mg N = 14
ISL	C_{max}, ng/mL	18.4 (42.3)	–	17.7 (42.4)
	T_{max}, h	0.583 (0.50, 1.00)	–	0.783 (0.50, 1.00)
	C_{8h}, ng/mL	1.80 (58.7)[a]	–	1.38 (28.8)
	C_{trough}, ng/mL	–	–	0.169 (55.5)
	$AUC_{0\text{-}8h}$, h·ng/mL	52.0 (25.6)[a]	–	42.2 (18.7)
	AUC_{tau}, h·ng/mL	–	–	131 (74.7)
LEN	C_{max}, ng/mL	46.4 (62.4)	183 (103)	99.2 (72.6)
	T_{max}, h	7.97 (4.00, 24.0)	6.18 (6.00, 7.93)	6.00 (4.00, 6.17)
	C_{8h}, ng/mL	39.0 (64.2)	151 (84.2)	82.2 (78.4)
	C_{trough}, ng/mL	–	–	35.9 (60.5)[b]
	$AUC_{0\text{-}8h}$, h·ng/mL	235 (64.5)	1040 (104)	625 (76.6)
	AUC_{tau}, h·ng/mL	–	–	9730 (73.9)[b]

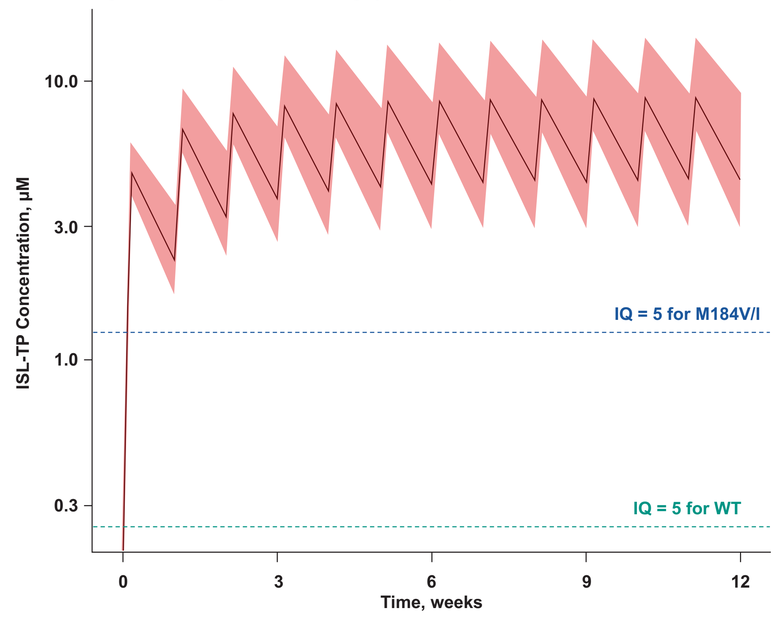
$AUC_{0\text{-}8h}$, area under the concentration-time curve from time 0 to 8 hours; AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{8h}, concentration 8 hours after dosing; C_{max}, maximum drug concentration; C_{trough}, trough concentration; CV, coefficient of variation; ISL, islatravir; LEN, lenacapavir; PK, pharmacokinetics; T_{max}, time to maximum drug concentration.

PK parameters are presented as mean (%CV), except T_{max}, which is median (Q1, Q3).

[a]n = 11; [b]n = 13.

- Steady state mean LEN C_{trough} (35.9 ng/mL; **Table 2**) remained well above IQ4 (15.5 ng/mL) and IQ1 (3.87 ng/mL)

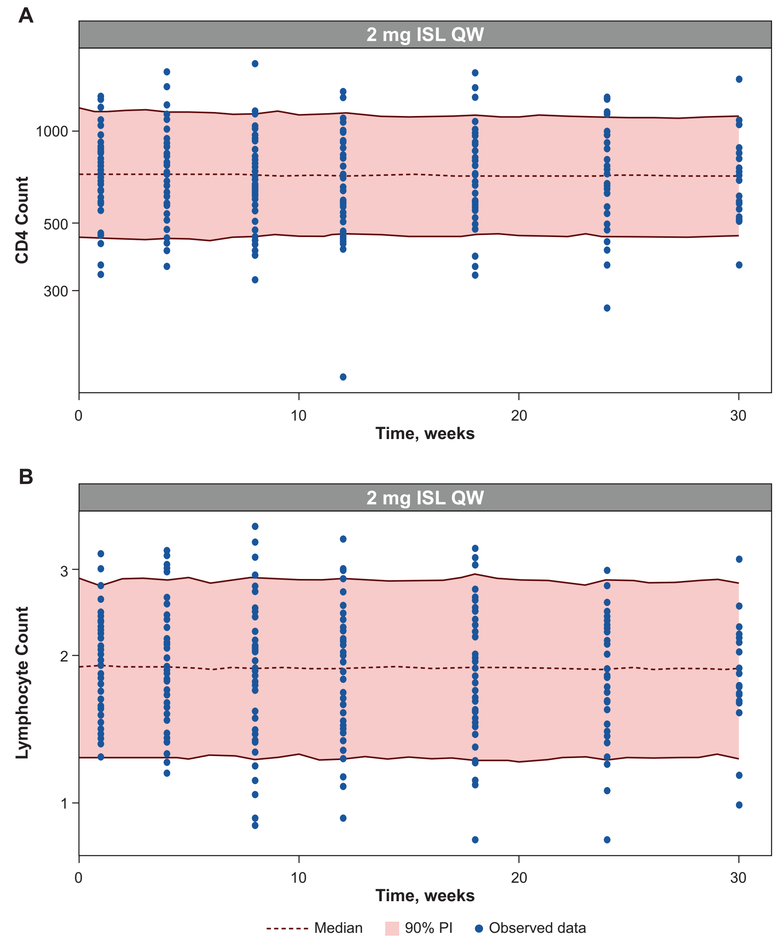
Figure 2. Simulations of ISL-TP concentration time series following ISL 2 mg QW dosing (n = 52)



IQ, inhibitory quotient; ISL-TP, islatravir triphosphate; QW, once weekly; WT, wild type.
Solid lines = median prediction; colored bands = 95% individual prediction interval.

- Based on popPK model projections, steady state mean ISL-TP C_{trough} (5.60 μM) remained well above the inhibitory quotient of 5 (IQ5; 1.25 μM) for M184V/I variants and the IQ5 (0.25 μM) for wild-type HIV-1 (**Figure 2**)
- PK/PD simulations demonstrated a lack of ISL-TP exposure–related decreases in CD4+ T-cell and lymphocyte counts in ISL+LEN–treated participants (**Figure 3**)

Figure 3. Model-predicted (shaded area) and observed (data points) (A) CD4+ T cell and (B) lymphocyte counts from ISL 2 mg QW dosing



ISL, islatravir; PI, prediction interval; QW, once weekly.
n = 1000*, reps = 100; *1000 sampled from the GS-US-563-6041 population (n = 52)
CD4+ T-cell count = cells/mm^3; lymphocyte cell count = 10^3 cells/mm^3

Conclusions

- Based on the plasma PK observed in this study, ISL 2 mg QW is predicted to produce ISL-TP exposure sufficient to cover wild-type HIV-1 and M184V/I variants with no negative impact on CD4+ T-cell or lymphocyte counts
- LEN 300 mg QW resulted in efficacious LEN exposure, consistent with approved subcutaneous LEN[8]
- These results are consistent with previous model-based predictions[9] and support ISL/LEN QW dosing in phase 3 clinical trials (NCT06630286; NCT06630299)

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