Pharmacokinetic Modeling of Missed Dose Scenario of Oral Weekly Islatravir Plus Lenacapavir

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Conclusions

- Simulations demonstrated that people with HIV-1 (PWH) who miss one dose of the 2/300 mg islatravir (ISL)/lenacapavir (LEN) fixed-dose combination (FDC) can resume treatment within one week to maintain efficacious drug concentrations, allowing for a one-week forgiveness window

Plain Language Summary

- Medicines to treat HIV need to stay at the right level in the body to work properly
  - Missing doses can cause the medicine levels to drop too low, which might allow the HIV virus to spread in the blood, and can raise the chance of HIV becoming resistant to the medicine (this means the medicine stops working)
- Islatravir (a new medicine being studied for HIV treatment) and lenacapavir (a medicine approved for HIV treatment) are being looked at in Phase 3 studies in people with HIV who do not have detectable levels of HIV in their blood (this is called being virologically suppressed)
  - Many treatments for HIV involve taking medicine every day, but islatravir and lenacapavir can be taken as a combined single tablet once a week to treat HIV
- We used computer models to look at what happens to the levels of islatravir and lenacapavir in the body if someone misses a dose. These model are used by scientists to work out how long after missing a dose should the next dose be taken to make sure there is enough medicine to work in the body
- We found that if people who miss one dose of islatravir plus lenacapavir take the next dose within one week, the level of these medicines in the body will still be high enough to be effective at treating HIV

Background

- Once-daily oral combination regimens are standard-of-care for treatment of HIV-1[1]
  - Lifelong adherence to antiretroviral therapies (ART) to reduce the risk of virologic failure is challenging for many PWH,[2] and novel, long-acting oral ARTs remain an unmet need[3]
- ISL is a nucleoside reverse transcriptase translocation inhibitor being investigated as an HIV-1 therapy[4]
  - ISL is converted intracellularly to the active ISL-triphosphate (ISL-TP) that potently inhibits HIV-1 replication by preventing translocation of reverse transcriptase on the viral primer template
- LEN is a first-in-class, multistage, selective inhibitor of HIV-1 capsid function with potent antiviral activity, and a novel resistance profile[5]
  - LEN inhibits HIV-1 at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of pre-integration complexes and impairing virion production and proper capsid core formation
- Phase 1 study results indicate that ISL/LEN FDC tablets had no significant effects on overall bioavailability or extent of absorption compared with single-agent tablets, and no drug-drug interaction was detected when the two agents were combined[6]
  - Therefore, single-agent ISL and LEN models are reasonable for projecting exposure outcomes of various dosing scenarios
- In a Phase 2 study (NCT05052996), following starting doses[a], a once-weekly (QW) oral regimen of 2 mg ISL plus 300 mg LEN maintained a high rate (94.2%) of viral suppression (HIV-1 RNA <50 copies/mL) at 48 weeks in PWH who were virologically suppressed[7,8]
- In two Phase 3 studies (NCT06630286; NCT06630299), following starting doses[b], a QW maintenance dose of oral 2/300 mg ISL/LEN FDC (one tablet) starting on Day 8 is being evaluated in virologically-suppressed PWH who have switched from standard-of-care treatment[9,10]
- Using simulation analyses with existing ISL and LEN population pharmacokinetic (PopPK) models, we report data to support effective drug concentrations within safety and efficacy margins in the event of missed oral QW ISL/LEN doses

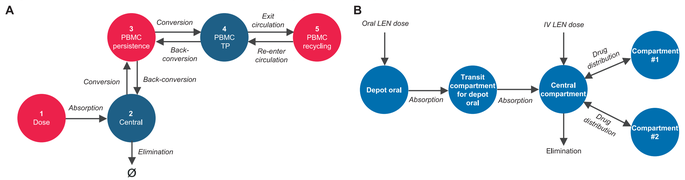
Objective

- We utilized PopPK modeling and simulation to evaluate pharmacokinetics (PK) of ISL and LEN following missed oral QW doses to quantify the degree of forgiveness for missed doses, and to inform make-up dosing strategies across various dosing scenarios

Methods

- ISL-TP simulations used an existing PopPK model developed using oral ISL PK data from ISL Phase 1–3 studies (**Figure 1A**)
- LEN simulations used an existing PopPK model developed with intravenous, oral, and subcutaneous LEN PK data from Phase 1–3 studies (**Figure 1B**)

Figure 1. Structural PopPK Models for ISL (A) and LEN (B)



ISL, islatravir; IV, intravenous; LEN, lenacapavir; PBMC, peripheral blood mononuclear cell; PopPK, population pharmacokinetics; TP, triphosphate.

- Simulations under steady-state conditions were performed to estimate the impact of various durations of missed doses and make-up-dose strategies
  - The reference scenario of no missed doses was clinical dosing with starting doses[b], followed by 2 mg ISL and 300 mg LEN (one tablet of 2/300 mg ISL/LEN FDC) QW starting on Day 8 as a maintenance dose
    - This is the same dosing utilized in the ongoing Phase 3 studies[9,10]
  - Simulation scenarios (**Figure 2**) were selected to include the specific scenarios that would provide the largest potential excursions in the maximum concentration (C_{max}) and the concentration at the end of the dosing interval (C_{trough}) in the event of missed or delayed doses
  - The same missed dose simulation scenarios were conducted for both ISL and LEN, given that the Phase 3 studies utilize a FDC formulation of the two drugs

Figure 2. Simulated Dosing Scenarios

No missed doses	**Scenario 1**	• No missed doses • Reference scenario with 2 mg ISL, 300 mg LEN QW
One missed dose	**Scenario 2a**	• Missed one maintenance dose with make-up dose taken on D10 after last maintenance dose and next scheduled dose is resumed
	Scenario 2b	• Missed one maintenance dose with make-up dose taken on D13 after last maintenance dose and next scheduled dose is resumed
	Scenario 3	• Missed one maintenance dose and resume usual maintenance dose 14 days after the last maintenance dose with no make-up doses in between
Two missed doses	**Scenario 4**	• Missed two maintenance doses >14 days from the last maintenance dose • Reload on D15 and D16 (1 mg ISL, 600 mg LEN each day) after last maintenance dose then continue regular QW maintenance doses (2 mg ISL, 300 mg LEN)

D, day; ISL, islatravir; LEN, lenacapavir; QW, once-weekly.

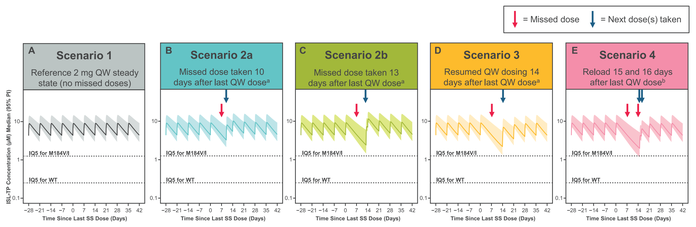
- Various dosing scenarios under steady-state conditions following missed oral QW doses were compared against the reference scenario of no missed doses (Scenario 1), as well as efficacy and clinically established safety exposure thresholds, as appropriate
  - For ISL-TP, the target was to ensure that the 95% prediction interval (PI) for ISL-TP concentrations remained:
    - Above the inhibitory quotient (IQ) 5 (1.25 µM) for M184V/I variants and IQ5 (0.25 µM) for wild-type HIV-1[11]
    - Below exposures associated with the 3 mg QW dose predicted in previous modeling and simulation analyses to have no meaningful impact on lymphocyte and CD4+ T-cell counts[12]
  - For LEN, the target was to ensure that the 90% confidence interval for mean LEN concentrations remained:
    - Above the IQ4 (15.5 ng/mL)[13]
    - Below the highest exposure with no associated safety signal, as established in the LEN Thorough-QT study[5]

Results

ISL Simulations

- Simulated ISL-TP concentrations for the reference scenario and missed dose scenarios are shown in **Figure 3A–E**; ISL-TP C_{trough} and C_{max} are summarized in **Table 1**
  - Transient increases in ISL-TP exposures that occurred in Scenario 2a and Scenario 2b, where two 2 mg doses of ISL are taken within a 1-week period, resulted in C_{max} values above the steady-state C_{max} with the 2 mg QW reference scenario. It was also well below the steady state C_{max} values associated with 3 mg QW, the dose predicted in previous modeling and simulation analyses to have no meaningful impact on lymphocyte counts (**Figures 3B–C and Table 1**)
  - ISL-TP maintained effective concentrations 1 week after a missed dose at steady state in Scenario 3, where dosing is resumed 14 days from the last dose with no make-up doses in between (**Figure 3D and Table 1**)
  - Reloading with 1 mg ISL on Day 15 and 1 mg ISL on Day 16, followed by QW maintenance doses in Scenario 4 also maintained effective concentrations (**Figure 3E and Table 1**)

Figure 3. Dose Simulation Plots for ISL: No Missed Doses (A), Missed Dose Scenario 2a (B), 2b (C), 3 (D), and 4 (E)



Red arrows indicate a missed dose, blue arrows indicate the next dose(s) taken. [a]Maintenance FDC (2 mg ISL) is used for Scenarios 2a, 2b, and 3. [b]Starting FDC (1 mg ISL) is used for Scenario 4.
FDC, fixed-dose combination; IQ, inhibitory quotient; ISL, islatravir; ISL-TP, islatravir-triphosphate; PI, prediction interval; QW, once-weekly; SS, steady state; WT, wild-type.

Table 1. Predicted ISL-TP C_{trough} and C_{max}

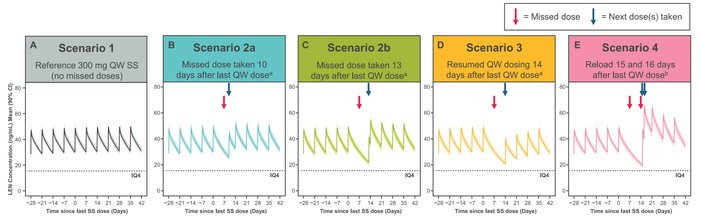
Scenario Median (95% PI), µM	ISL-TP C_{trough}	ISL-TP C_{max}
Scenario 1: Reference 2 mg QW steady state (no missed doses)	4.42 (2.95–9.10)	9.11 (6.97–15.0)
Scenario 2a: Missed dose taken 10 days after last QW dose[a]	3.21 (2.03–7.30)	10.1 (7.81–16.1)
Scenario 2b: Missed dose taken 13 days after last QW dose[a]	2.38 (1.43–5.91)	11.5 (9.14–17.5)
Scenario 3: Resumed QW dosing 14 days after last QW dose	2.16 (1.28–5.52)	N/A[b]
Scenario 4: Reload 15 and 16 days after last QW dose	1.97 (1.15–5.17)	N/A[b]

For reference, predicted median (95% PI) ISL-TP C_{max} for 3 mg QW ISL was 13.7µM (10.5–22.5); no meaningful impact on lymphocyte and CD4+ T cell counts were predicted for 3 mg QW ISL in previous modeling and simulation analyses.[12]
[a]In these scenarios, the maximum predicted ISL-TP concentration occurs following the "regular" 2 mg ISL dose given after the "make-up" dose. [b]C_{max} values after the make-up dose were below 2 mg QW ISL C_{max} values.
C_{max}, maximum concentration; C_{trough}, concentration at the end of the dosing interval; ISL, islatravir; ISL-TP, islatravir-triphosphate; PI, prediction interval; QW, once-weekly.

LEN Simulations

- Simulated LEN concentrations for the reference scenario and missed dose scenarios are shown in **Figure 4**; LEN C_{trough} and C_{max} are summarized in **Table 2**
  - Simulated mean C_{trough} concentrations were above the target concentration of 15.5 ng/mL (IQ4) for each scenario (**Figure 4A–E**)
  - LEN has been shown to be well tolerated with a wide safety margin, with no clinically relevant prolongation of the QTcF interval at concentrations up to 9-fold higher than therapeutic exposures.[5] Therefore, the potential increases in C_{max} from various dosing scenarios, including following re-loading as per Scenario 4 (**Figure 4E**), are not anticipated to pose additional safety risks

Figure 4. Dose Simulation Plots for LEN: No Missed Doses (A), Missed Dose Scenario 2a (B), 2b (C), 3 (D), and 4 (E)



Red arrows indicate a missed dose, blue arrows indicate the next dose(s) taken. [a]Maintenance FDC (300 mg LEN) is used for Scenarios 2a, 2b, and 3. [b]Starting FDC (600 mg LEN) is used for Scenario 4.
CI, confidence interval; FDC, fixed-dose combination; IQ, inhibitory quotient; LEN, lenacapavir; QW, once-weekly; SS, steady state.

Table 2. LEN C_{trough} and C_{max} for Various Dosing Scenarios at Steady State With QW Maintenance Dosing

Scenario Mean (90% CI), ng/mL	LEN C_{trough}	LEN C_{max}
Scenario 1: Reference 300 mg QW steady state (no missed doses)	29.9 (27.7–32.4)	48.9 (45.7–53.2)
Scenario 2a: Missed dose taken 10 days after last QW dose	25.6 (23.7–27.9)	52.1 (47.8–56.5)[a]
Scenario 2b: Missed dose taken 13 days after last QW dose	21.9 (20.2–24.0)	55.6 (51.3–58.7)[a]
Scenario 3: Resumed QW dosing 14 days after last QW dose	20.7 (19.4–22.9)	N/A[b]
Scenario 4: Reload 15 and 16 days after last QW dose	19.6 (17.8–21.6)	67.7 (62.4–72.4)[c,d]

[a]In these scenarios, predicted LEN C_{max} occurs following the "regular" 300 mg LEN dose given after the "make-up" dose. [b]C_{max} values after the make-up dose were below LEN 300 mg QW C_{max} values. [c]C_{max} values after the second 600 mg oral re-loading dose are presented. [d]Potential increases in C_{max} in Scenario 4 are not anticipated to be associated with additional risk given that LEN has been shown to be well-tolerated with a wide safety margin, with no clinically relevant prolongation of the QTcF interval at concentrations up to 9-fold higher than therapeutic exposures (mean LEN C_{trough} and C_{max}, respectively, are 46.9 and 88.0 ng/mL for Days 1 to 15 [oral loading period] and 32.5 and 86.5 ng/mL for Day 15 to end of Month 6).[5]
CI, confidence interval; C_{max}, maximum concentration; C_{trough}, concentration at the end of the dosing interval; LEN, lenacapavir; N/A, not applicable; QW, once-weekly.

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DL, RV, RM, CL, and **GG** are 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.
MI, HZ, HD-S, MSR, and **DDM** are all employees and shareholders of Gilead Sciences, Inc.
NVM at the time of study conduct and data analysis was an employee and shareholder of Gilead Sciences, Inc. **NVM** is now an employee of Eli Lilly and Company.

Footnotes:
[a]2 mg ISL on Day 1 and 600 mg LEN on Days 1 and 2
[b]1 mg ISL and 600 mg LEN on Days 1 and 2 (two tablets of 0.5/300 mg ISL/LEN FDC on each day)