Commonly Prescribed Concomitant Medications and Clinical Safety Findings With Lenacapavir for Pre-Exposure Prophylaxis in PURPOSE 2

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Conclusions

- There was no difference in rates of common adverse events (AEs) associated with phosphodiesterase type 5 (PDE5) inhibitors or statins between participants who did and did not use them together with lenacapavir (LEN) for pre-exposure prophylaxis (PrEP), even though LEN may increase concentrations of coadministered medications, such as PDE5 inhibitors and some statins, that are metabolized via cytochrome P450 3A (CYP3A)
  - Rates of AEs associated with PDE5 inhibitor/statin use were low overall with the recommended dose adjustments per study protocol
- LEN, like other moderate CYP3A inhibitors, can be safely coadministered with PDE5 inhibitors and statins with appropriate monitoring and, in some cases, dose adjustment

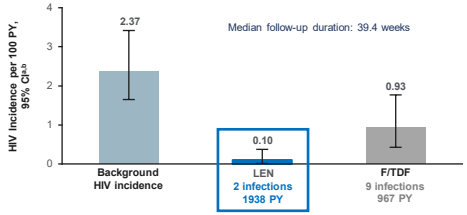
Plain Language Summary

- Human immunodeficiency virus (HIV) prevention medication, also known as pre-exposure prophylaxis (or "PrEP"), helps to lower the chances of getting HIV
- Lenacapavir (LEN) is a long-acting type of PrEP that is given as an injection twice a year (every 6 months)
- In a clinical trial called PURPOSE 2, LEN worked very well to protect cisgender men, transgender women, transgender men, and gender nonbinary individuals who have sex with men from getting HIV
- LEN can slightly increase the amount of certain other medicines in the blood if they are taken together, including:
  - Phosphodiesterase type 5 (PDE5) inhibitors (used for erectile dysfunction)
  - Some statins (used to lower cholesterol levels)
- The higher blood levels of these other medicines can increase the chances of having side effects, like:
  - Prolonged or painful erections, low blood pressure, fainting, or vision changes (with PDE5 inhibitors)
  - Muscle pain, muscle damage, or changes in levels of liver enzymes (with statins)
- In the PURPOSE 2 study:
  - Side effects that are commonly seen with PDE5 inhibitors or statins were rare
  - None of the people taking PDE5 inhibitors with LEN had any of these side effects
  - Among those taking statins with LEN, only one person reported muscle spasms and one reported changes in liver enzyme levels
- These results suggest that LEN can be safely used with PDE5 inhibitors or statins as long as healthcare providers regularly check and adjust the dosage if needed

Introduction

- PURPOSE 2 (NCT04925752) demonstrated superior efficacy of twice-yearly subcutaneous (SC) LEN versus daily oral emtricitabine/tenofovir disoproxil fumarate (F/TDF) as PrEP among cisgender men, transgender women, transgender men, and gender nonbinary individuals who have sex with partners assigned male at birth (**Figure 1**)[1]

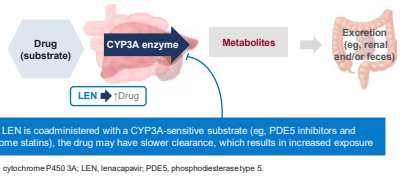
Figure 1. Incidence of HIV Infections in PURPOSE 2[1]



[a]Overall n: background HIV incidence group, 4634; LEN, 2179; F/TDF, 1086.
[b]95% CIs: background HIV incidence group, 1.649-3.417; LEN, 0.012-0.373; F/TDF, 0.426-1.768.
CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; PY, person-years.

- LEN is a moderate inhibitor of CYP3A (**Figure 2**)[2,3]
  - Coadministered drugs that are metabolized by CYP3A (such as PDE5 inhibitors and statins) may therefore have slower clearance

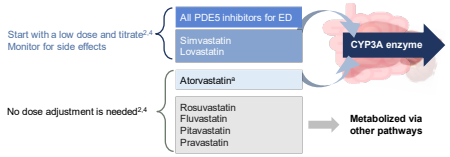
Figure 2. LEN, a Moderate Inhibitor of CYP3A, May Increase Blood Levels of Coadministered Drugs That Are CYP3A Substrates[2,4]



CYP3A, cytochrome P450 3A; LEN, lenacapavir; PDE5, phosphodiesterase type 5.

- LEN may thus increase blood levels of coadministered medications that are metabolized by CYP3A, such as PDE5 inhibitors and some statins (**Figure 3**)[2]

Figure 3. PDE5 Inhibitors and Statins That Are Metabolized by CYP3A[2,5]



[a]Although atorvastatin is metabolized by CYP3A, exposure is not impacted by coadministration with a moderate CYP3A inhibitor such as LEN because it is not a sensitive substrate of CYP3A.
CYP3A, cytochrome P450 3A; ED, erectile dysfunction; PDE5, phosphodiesterase type 5.

- Erectile dysfunction (ED) drugs such as PDE5 inhibitors may be used by people who could benefit from PrEP, including healthy young men without ED[6,9]
  - Recreational use of PDE5 inhibitors has been reported by 22% of healthy young men[6] and 34% of gay and bisexual men[7]
  - PDE5 inhibitor use has been reported in 12% to > 40% of PrEP users[8,9]

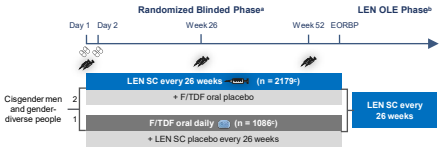
Objective

- To determine whether the rates of common AEs associated with PDE5 inhibitors or statins increased when these drugs were coadministered with LEN in PURPOSE 2

Methods

- PURPOSE 2 was a Phase 3, double-blind, randomized controlled trial in which participants were randomized 2:1 to receive twice-yearly SC LEN or daily oral F/TDF (**Figure 4**)
- Participants were seen at Weeks 4, 8, 13, and every 13 weeks thereafter; assessments for AEs occurred at each visit

Figure 4. PURPOSE 2 Study Design[1]



Study population: Cisgender men and gender-diverse people ≥ 16 years old who are at risk of HIV acquisition[d]

Present analysis objectives

- To determine whether the rates of common AEs associated with PDE5 inhibitors or statins reported during the randomized blinded phase increased when these drugs were coadministered with LEN in PURPOSE 2

[a]Participants randomized to LEN received loading doses of two 300-mg tablets of LEN on each of Days 1 and 2 and SC LEN 927 mg on Day 1 and then every 26 weeks (± 7 days); participants randomized to F/TDF received matched placebos at these times.
[b]Participants randomized to LEN in the RBP who chose to participate in the LEN OLE Phase received SC LEN every 26 weeks (± 7 days) and had study visits every 13 weeks (± 7 days). Participants randomized to F/TDF in the RBP who chose to participate in the LEN OLE phase received SC LEN on LEN OLE Day 1 and every 26 weeks thereafter; these participants also received an oral LEN loading dose on LEN OLE Days 1 and 2 and had study visits at LEN OLE Day 1, Weeks 4 and 8 (± 2 days), Week 13 (± 7 days), and then every 13 weeks (± 7 days) thereafter.
[c]Included in the full analysis set for primary efficacy analyses.
[d]Cisgender men, transgender women, transgender men, and gender nonbinary individuals who have condomless receptive anal sex with partners assigned male at birth.
AE, adverse event; EORBP, end of randomized blinded phase; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; OLE, open-label extension; PDE5, phosphodiesterase type 5; RBP, randomized blinded phase; SC, subcutaneous.

- Dose adjustments and/or monitoring of concomitant medications with potential drug-drug interactions with LEN were recommended during the study (**Table 1**)
- The frequency of AEs commonly associated with increased statin or PDE5 inhibitor exposure was assessed by study drug and baseline PDE5 inhibitor/statin use in the overall study population
  - PDE5 inhibitor-associated AEs: Priapism, painful erection, hypotension, syncope, vision changes, and hearing loss
  - Statin-associated AEs: Myalgia, rhabdomyolysis, muscle pain or discomfort, increased creatine phosphokinase levels, and increased liver function test values

Table 1. PURPOSE 2 Protocol Guidance on Coadministration of PDE5 Inhibitors and Statins With LEN

Coadministered Drug	Interaction Potential With LEN	Dosing Recommendations
PDE5 inhibitors	Concentrations of PDE5 inhibitors may increase with LEN	• Maximum permitted doses: – Sildenafil ≤ 25 mg in 48 hours – Vardenafil ≤ 2.5 mg in 72 hours – Tadalafil ≤ 10 mg in 72 hours
Statins	Concentrations of some statins may increase with LEN • Careful monitoring of signs or symptoms of muscle weakness or myopathy is recommended	• Maximum permitted doses: – Simvastatin 10 mg – Lovastatin 20 mg – Atorvastatin[a] 40 mg

[a]This maximum dose was recommended in the study out of caution for a potential drug-drug interaction, but an *a priori* dose adjustment of atorvastatin is not needed with LEN because it is a moderate, and not a sensitive, CYP3A substrate.
CYP3A, cytochrome P450 3A; LEN, lenacapavir; PDE5, phosphodiesterase type 5.

Results

- At baseline:
  - PDE5 inhibitor use was reported by 29/2183 (1.3%) participants receiving LEN and 16/1088 (1.5%) receiving F/TDF
  - Statin use was reported by 40/2183 (1.8%) participants receiving LEN and 24/1088 (2.2%) receiving F/TDF
- Frequency of common AEs associated with PDE5 inhibitors and statins are summarized in **Tables 2** and **3**
- No PDE5 inhibitor-associated AEs were reported among participants receiving PDE5 inhibitors at baseline
- Among participants receiving statins at baseline:
  - Muscle spasms were reported by 1 (2.5%) participant in the LEN arm; muscle spasms and pain in extremity were each reported by 1 (4.2%) participant in the F/TDF arm
  - Increased liver enzymes were reported by 1 (2.5%) participant in the LEN arm and none in the F/TDF arm
  - Myalgia, rhabdomyolysis, and increased creatine phosphokinase levels were not reported

Table 2. No Increase in Common AEs Associated With PDE5 Inhibitors in PURPOSE 2

	All Participants (N = 3271)			
	Baseline PDE5 Inhibitor Use			
	Yes (n = 45)		No (n = 3226)	
	LEN (n = 29)	F/TDF (n = 16)	LEN (n = 2154)	F/TDF (n = 1072)
Priapism	0	0	0	1 (< 0.1)
Painful erection	0	0	0	1 (< 0.1)
Hypotension	0	0	2 (< 0.1)	2 (0.2)
Syncope	0	0	17 (0.8)	14 (1.3)
Vision change[a]	0	0	4 (0.2)	0
Hearing loss[b]	0	0	1 (< 0.1)	0

Data are n (%). AEs are based on AE Preferred Terms coded using MedDRA, Version 27.0.
[a]Includes vision blurred, visual acuity reduced, and vision impairment.
[b]Hearing loss based on the AE high-level term.
AE, adverse event; LEN, lenacapavir; MedDRA, Medical Dictionary for Regulatory Activities; PDE5, phosphodiesterase type 5; F/TDF, emtricitabine/tenofovir disoproxil fumarate.

Table 3. No Increase in Common AEs Associated With Statins in PURPOSE 2

	All Participants (N = 3271)			
	Baseline Statin Use			
	Yes (n = 64)		No (n = 3207)	
	LEN[a] (n = 40)	F/TDF[b] (n = 24)	LEN (n = 2143)	F/TDF (n = 1064)
Myalgia	0	0	32 (1.5)	13 (1.2)
Rhabdomyolysis	0	0	4 (0.2)	1 (< 0.1)
Muscle/extremity pain or discomfort[c]	1 (2.5)	2 (8.3)	12 (0.6)	7 (0.7)
Increased CPK	0	0	7 (0.3)	5 (0.5)
Increased liver enzymes[d]	1 (2.5)	0	14 (0.7)	8 (0.8)

Data are n (%). AEs are based on AE Preferred Terms coded using MedDRA, Version 27.0.
[a]Atorvastatin (n = 17), rosuvastatin (n = 15), simvastatin (n = 10). Number of summed participants differs from total if participants switched treatments.
[b]Atorvastatin (n = 14), rosuvastatin (n = 6), simvastatin (n = 5). Number of summed participants differs from total if participants switched treatments.
[c]Includes pain in extremity, musculoskeletal pain, musculoskeletal discomfort, and muscle spasms.
[d]Increases reported as AEs, not based on reported laboratory tests; includes hypertransaminasemia, increased ALT, increased AST, increased hepatic enzymes, abnormal transaminases, increased bilirubin, increased unconjugated bilirubin, and hyperbilirubinemia.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; LEN, lenacapavir; MedDRA, Medical Dictionary for Regulatory Activities; F/TDF, emtricitabine/tenofovir disoproxil fumarate.

Study Limitations

- The numbers of participants reporting concomitant PDE5 inhibitor or statin use were low, as were the rates of common AEs associated with statin/PDE5 inhibitor use
- Any baseline statin use was included in this analysis, regardless of whether the statin was a CYP3A substrate
- AE causality cannot be determined from this dataset and AEs may be attributable to causes other than concomitant medication use

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