Favorable Adherence and Safety of Twice-Yearly Subcutaneous Lenacapavir for PrEP Among PURPOSE 2 Participants Who Used Substances

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Acknowledgments and Disclosures

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- Gilead Sciences, Inc., funded the study and designed the study with input from the PIs and G-CAG. The PIs and study staff gathered data; Gilead Sciences, Inc., monitored conduct of the trial, received the data, and performed analyses. The PURPOSE 2 Study Team all vouch for the data and analysis
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- All relevant financial disclosures have been mitigated

G-CAG, Global Community Advisory Group; **PI**, principal investigator.

Twice-Yearly Lenacapavir for PrEP is Highly Efficacious

Cisgender men and gender-diverse individuals who have sex with men and who use substances are among the most vulnerable for acquiring HIV[1,2]

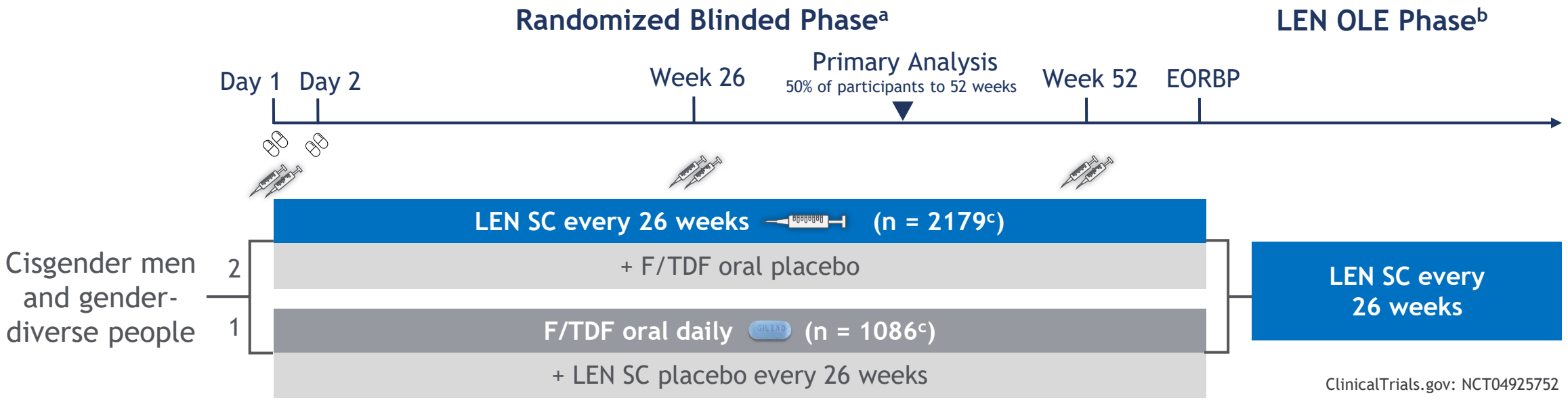
- Overlapping social, structural, and individual barriers make daily PrEP adherence challenging for people who use substances[3,4]
- In PURPOSE 2, twice-yearly SC LEN for PrEP showed high efficacy and safety,[5] including in people who use substances
- Twice-yearly LEN may offer a favorable alternative to existing PrEP choices for people who use substances
- As LEN is a moderate CYP3A inhibitor[6] and fentanyl is partially metabolized by CYP3A,[7] an increase in fentanyl concentration with LEN may be possible

We investigated LEN adherence and safety in PURPOSE 2 participants who used substances, and evaluated the potential DDI between LEN and fentanyl

CYP, cytochrome P450; **DDI**, drug-drug interaction; **LEN**, lenacapavir; **PrEP**, pre-exposure prophylaxis; **SC**, subcutaneous.

1. Lauckner C, et al. *Curr HIV/AIDS Rep*. 2023;20:231-50. 2. UNAIDS. https://www.unaids.org/sites/default/files/media_asset/2024-unaids-global-aids-update-gay-men_en.pdf (accessed August 15, 2025). 3. Batchelder AW, et al. *Sex Health*. 2017;14:59-71.
4. Antonini M, et al. *Rev Bras Enferm*. 2023;76:e20210963. 5. Kelley CF, et al. *N Engl J Med*. 2025;392:1261-76. 6. Yeztugo USPI. Gilead Sciences, Inc. June 2025. 7. Sun H-L, et al. Poster PI-019 presented at: American Society for Clinical Pharmacology & Therapeutics (ASCPT) Annual Meeting; May 28-31, 2025; Washington, DC, USA.

PURPOSE 2 Study Design



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

Present analysis objectives

- LEN adherence and rates of AEs in participants who used substances
- Evaluation of potential DDI between LEN and fentanyl

[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 (additional participants are included in the safety analysis). [d]Cisgender men, transgender women and men, and non-binary people aged ≥ 16 years who have condomless receptive anal sex with partners assigned male at birth.

AE, adverse event; **DDI**, drug-drug interaction; **EORBP**, end of randomized blinded phase; **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **LEN**, lenacapavir; **OLE**, open-label extension; **RBP**, randomized blinded phase; **SC**, subcutaneous.

Kelley CF, et al. *N Engl J Med*. 2025;392:1261-76.

We Assessed LEN Safety and Adherence by Drug Use or Binge Drinking and the Potential for DDI With Fentanyl

- Data on self-reported substance use were collected at baseline for this analysis:

Substance Use Type	Definition
Any drug use in the 12 weeks prior to baseline (including oral, injection, and inhalation)	• Cocaine, amphetamine-type stimulants, inhalants, sedatives or sleeping pills, hallucinogens, opioids, and prescription drugs for nonprescription purpose • Cannabis use was excluded
Binge drinking	• Monthly or more frequent consumption of ≥ 6 drinks on one occasion reported at baseline

- Adherence was defined as on-time injections ≤ 28 weeks from the last injection
- AEs were compared across participants reporting different types of substance use and those reporting no substance use

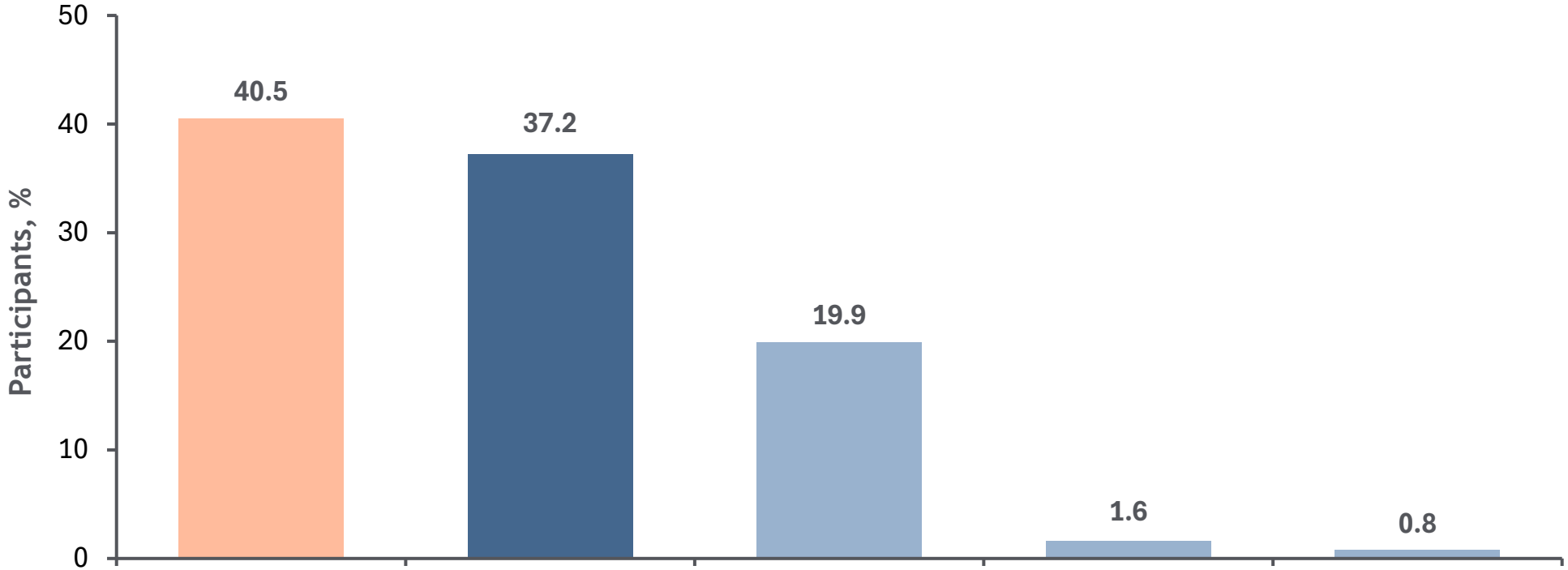
AE, adverse event; **DDI**, drug-drug interaction.

More than a Third of PURPOSE 2 Participants Receiving LEN Reported Any Drug Use and/or Binge Drinking

Characteristic	LEN (N = 2183)
Age, years, median (range)	28 (17–74)
Age 16 to ≤ 25 years, n (%)	752 (34.4)
Race, n/N (%)	
Black[a]	811/2175 (37.3)
White	722/2175 (33.2)
Asian	269/2175 (12.4)
Other[b]	373/2175 (17.1)
Hispanic or Latino/a, n/N (%)	1378/2182 (63.2)
Gender identity, n (%)	
Cisgender man	1697 (77.7)
Transgender woman	315 (14.4)
Transgender man	29 (1.3)
Gender nonbinary[c] and other[d]	142 (6.5)
Participants reporting any drug use,[e] n/N (%)	767/2061 (37.2)
Participants reporting binge drinking,[f] n/N (%)	841/2074 (40.5)

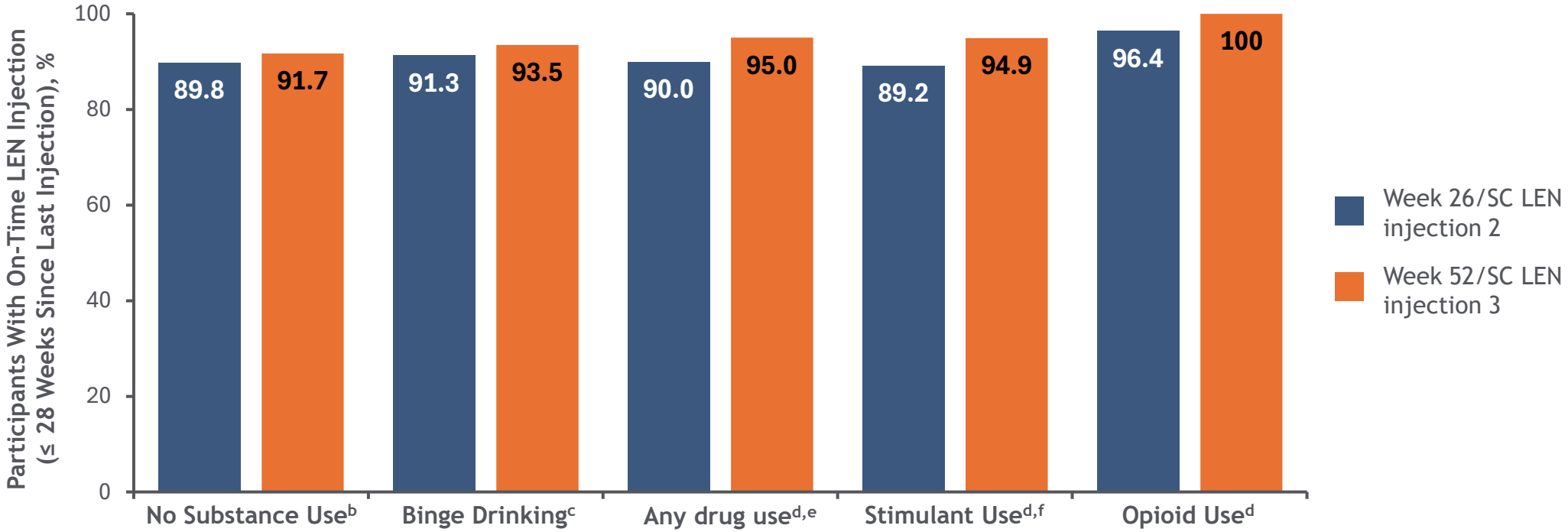
Baseline characteristics, including substance use, were similar across LEN and F/TDF groups. Race and ethnic groups were reported by the participants. [a]Included all participants who identified as being Black or of Black ancestry and included the terms "Black", "Black/White", "Black/Pardo" (Brazilian term for a specific racial category), "Black/Brown" (Brazil), "Black/Colored" (South African term for a specific racial category), "Black/American Indian or Alaska Native", "Black/Asian", and "Black/Native Hawaiian or Pacific Islander". [b]Included "American Indian or Alaska Native", "Native Hawaiian or Pacific Islander", "Asian/Native Hawaiian or Pacific Islander", "White/Native Hawaiian or Pacific Islander", "White/American Indian or Alaskan Native", "Asian/White", "Colored" (South Africa), "Pardo" (Brazil), "White/Brown" (Brazil), "multiracial any other", and "not multiracial other". [c]Among the participants who identified as gender nonbinary, 122/136 (89.7%) in the LEN group were assigned male at birth. [d]The "other" category included participants who identified as "Travesti" (3 in the LEN group) or as "other" gender (3 in the LEN group). [e]Includes cocaine, amphetamine-type stimulants, inhalants, sedatives or sleeping pills, hallucinogens, opioids, and prescription drugs for nonprescription purpose in the 12 weeks prior to baseline, and excludes cannabis use. [f]Monthly or more frequent consumption of ≥ 6 drinks on one occasion reported at baseline. **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **LEN**, lenacapavir.
The majority of data above were published in Kelley CF, et al. *N Engl J Med*. 2025;392:1261-76.

Over 40% of Participants Reported Monthly or More Frequent Binge Drinking Episodes and Approximately 37% Reported Drug Use



Substance use categories are not mutually exclusive. The number N is the number of individuals who answered each question. [a]Monthly or more frequent consumption of ≥ 6 drinks on one occasion reported at baseline. [b]In the 12 weeks prior to baseline. [c]Includes cocaine, amphetamine-type stimulants, inhalants, sedatives or sleeping pills, hallucinogens, opioids, and prescription drugs for nonprescription purpose, and excludes cannabis use. [d]Defined as use of cocaine or amphetamine-type stimulants.

Substance Use Did Not Impact Adherence to SC LEN Injections



	No Substance Use[b]		Binge Drinking[c]		Any drug use[d,e]		Stimulant Use[d,f]		Opioid Use[d]	
On-time injections	644	220	695	273	592	265	315	150	27	14
Number of participants expected to receive injection[a]	717	240	761	292	658	279	353	158	28	14

SC LEN adherence was high and comparable across substance use categories and with participants who did not report substance use

Sample limited to participants randomized and treated after the clinical hold was lifted. Substance use categories are not mutually exclusive. [a]The population presented is limited to participants with the potential to reach the corresponding injection visit at the time of the primary analysis and who did not permanently discontinue the randomized blinded phase prior to the end of the corresponding injection visit window. [b]Defined as participants who denied any drug use (excluding cannabis) and denied monthly or more frequent binge-drinking episodes. [c]Monthly or more frequent consumption of ≥ 6 drinks on one occasion reported at baseline. [d]In the 12 weeks prior to baseline. [e]Includes cocaine, amphetamine-type stimulants, inhalants, sedatives or sleeping pills, hallucinogens, opioids, and prescription drugs for nonprescription purpose, and excludes cannabis use. [f]Defined as use of cocaine or amphetamine-type stimulants. **LEN**, lenacapavir; **SC**, subcutaneous.

Frequency of AEs Was Similar Regardless of Substance Use

Participants, n (%)	No Substance Use[a] n = 822	Binge Drinking[b] n = 841	Any Drug Use[c,d] n = 767	Stimulant Use[c,e] n = 409	Opioid Use[c] n = 33
AEs (excluding injection-site reactions)	581 (70.7)	626 (74.4)	599 (78.1)	322 (78.7)	24 (72.7)
Grade ≥2	416 (50.6)	466 (55.4)	469 (61.1)	259 (63.3)	21 (63.6)
Grade ≥3	34 (4.1)	31 (3.7)	33 (4.3)	20 (4.9)	1 (3.0)
Serious AEs	28 (3.4)	22 (2.6)	24 (3.1)	16 (3.9)	1 (3.0)
Serious AEs related to study drug	0	0	0	0	0
Injection-site reactions to study SC injection	684 (83.2)	715 (85.0)	641 (83.6)	341 (83.4)	30 (90.9)
Death[f]	1 (0.1)	1 (0.1)	3 (0.4)	1 (0.2)	0

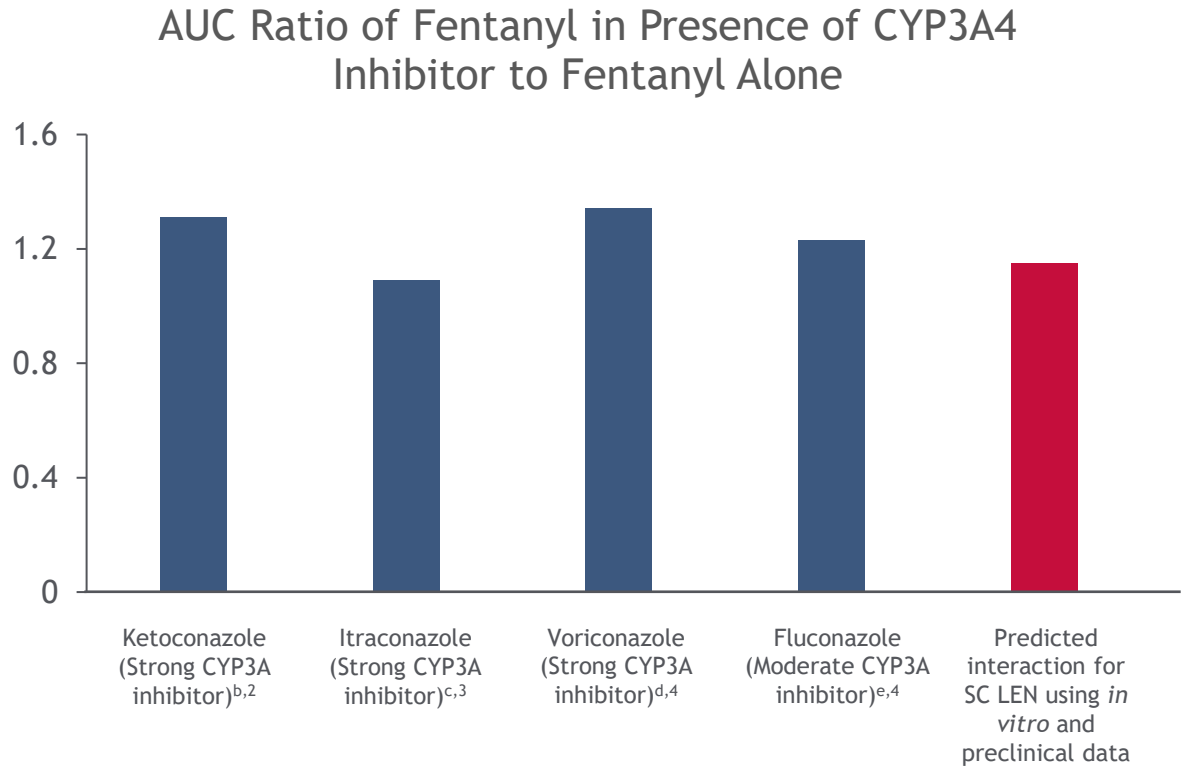
- The most common AEs (excluding injection-site reactions) were gonococcal, chlamydia, and upper respiratory tract infections
- Incidence of injection-site reactions was similar regardless of substance use

Substance use–related overdoses were not observed, and there were no study drug–related serious AEs reported

Substance use categories are not mutually exclusive. [a]Defined as participants who denied any drug use (excluding cannabis) in the 12 weeks prior to baseline and denied monthly or more frequent binge-drinking episodes. [b]Monthly or more frequent consumption of ≥ 6 drinks on one occasion reported at baseline. [c]In the 12 weeks prior to baseline. [d]Includes cocaine, amphetamine-type stimulants, inhalants, sedatives or sleeping pills, hallucinogens, opioids, and prescription drugs for nonprescription purpose, and excludes cannabis use. [e]Defined as use of cocaine or amphetamine-type stimulants. [f]Causes of death in the "no substance use" group: completed suicide (n = 1); in the "binge drinking" group: road traffic accident (n = 1); in the "any drug use" group: unknown (n = 1), road traffic accident (n = 1), cerebrovascular accident and pulmonary thromboembolism (n = 1); in the "stimulant use" group: unknown (n = 1). **AE**, adverse event; **SC**, subcutaneous.

Low Clinical Interactions Predicted Between SC LEN and Fentanyl

- Fentanyl metabolism occurs through multiple pathways in addition to CYP3A[1]
- When fentanyl is given in the presence of a strong CYP3A inhibitor, the C_{max} is unchanged, but AUC is slightly increased due to prolonged terminal elimination[2-7]
- *In vitro* data predicts a weak interaction between SC LEN and IV fentanyl (AUC ratio of 1.15)[1]
- A preliminary PBPK model suggests no clinically meaningful interaction between SC LEN and fentanyl[a]



Consistent with diverse fentanyl metabolism pathways, in vitro data, and previous literature on fentanyl metabolism and CYP3A inhibitors, preliminary PBPK modeling suggests minimal interaction

[a]Additional PBPK model validation is ongoing to confirm the interaction between SC LEN and fentanyl; [b]Ketoconazole (Strong CYP3A inhibitor; CYP2C8 inhibitor); [c]Itraconazole; [d]Voriconazole (Strong CYP3A inhibitor; moderate CYP2C19 inhibitor); [e]Fluconazole (Moderate CYP3A inhibitor; strong CYP2C19 inhibitor). 1. Sun H-L, et al. Poster PI-019 presented at: American Society for Clinical Pharmacology & Therapeutics (ASCPT) Annual Meeting; May 28-31, 2025; Washington, DC, USA. 2. Ziesenitz VC, et al. *J Clin Pharmacol*. 2015;55(6): 708-717. 3. Palkama VJ, et al. *Br J Anaesth*. 1998;81:598-600. 4. Saari TI, et al. *Eur J Clin Pharmacol*. 2008;64:25-30. 5. Yassen A, et al. *Clin Pharmacol Ther*. 2007;81:50-8. 6. Algera MH, et al. *Clin Pharmacol Ther*. 2021;109:637-45. 7. Balanza GA, et al. *PNAS Nexus*. 2022;1:158. **AUC**, area under the curve; **CYP**, cytochrome P450; **IV**, intravenous; **LEN**, lenacapvir; **PBPK**, physiologically-based pharmacokinetics; **SC**, subcutaneous.

Conclusions

- We observed high rates of on-time LEN injections and an acceptable safety profile among people who use drugs or binge drink
- No clinically relevant interactions between LEN and fentanyl are expected

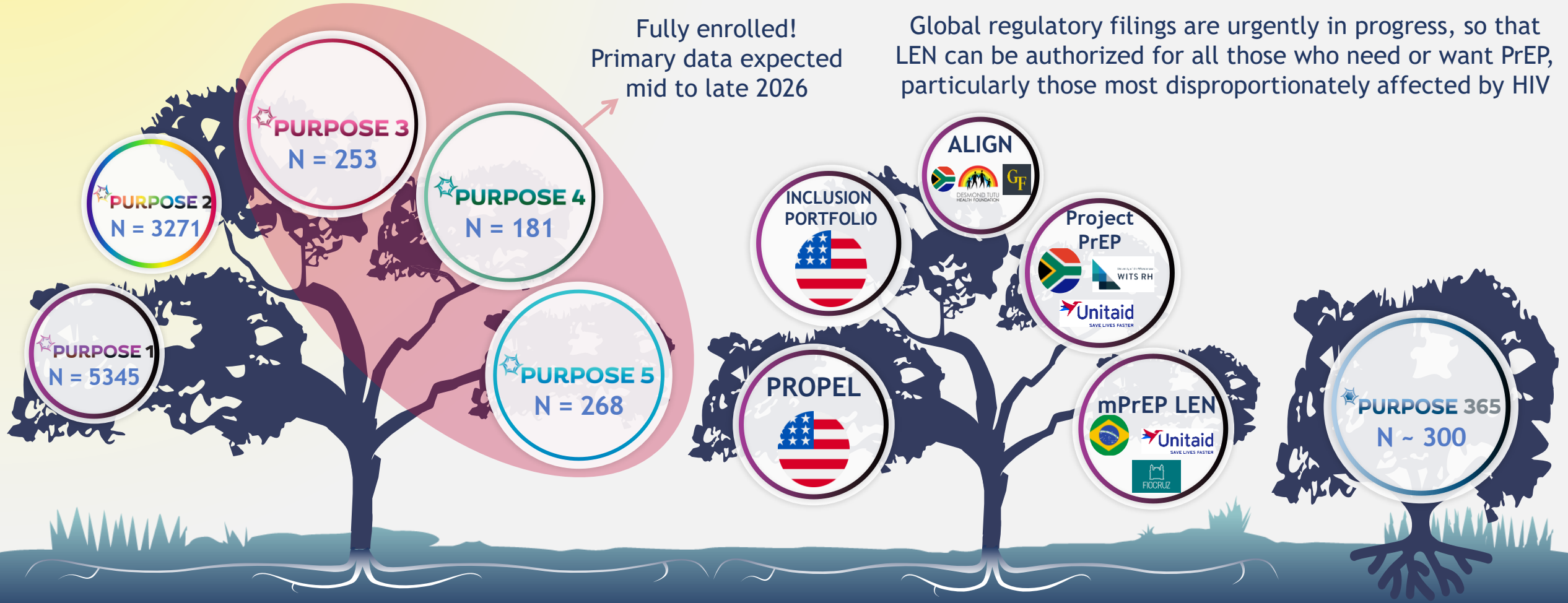
Twice-yearly SC LEN is a favorable option for people who use drugs or binge drink

LEN, lenacapavir; SC, subcutaneous.

A Growing PURPOSE Portfolio

Fully enrolled!
Primary data expected
mid to late 2026

Global regulatory filings are urgently in progress, so that LEN can be authorized for all those who need or want PrEP, particularly those most disproportionately affected by HIV



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PURPOSE 1: NCT04994509; PURPOSE 2: NCT04925752; PURPOSE 3: NCT06101329; PURPOSE 4: NCT06101342; PURPOSE 5: NCT06513312; PURPOSE 365: NCT07047716.
LEN, lenacapavir; **PrEP**, pre-exposure prophylaxis.

PURPOSE studies. https://www.purposestudies.com (accessed August 15, 2025).

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