PURPOSE

Prevention with PURPOSE

IAS 2025

Efficacy, Safety, and Pharmacokinetics of Twice-Yearly Subcutaneous Lenacapavir for PrEP Among Adolescents and Young People in the Phase 3 Trials PURPOSE 1 and PURPOSE 2

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Acknowledgments and Presenter Disclosures

Acknowledgments

I want to begin my talk by extending my deepest gratitude to the PURPOSE trial participants who have shared their time, experiences, and bodies for the purposes of this research, and their families and communities, the global community advisory and accountability groups, the site staff and investigators, and the members of the PURPOSE study teams. Much of the fight against HIV and AIDS relies upon people living with HIV and people who want or need PrEP continuing to put themselves forward and this research and our fight against HIV and AIDS is indebted to those past and present.

Disclosures

- Gilead Sciences funded the study and designed the study with input from the PIs and G-CAGs. The PIs and study staff gathered data; Gilead Sciences, Inc. monitored conduct of the trial, received the data, and performed analyses.
- Medical writing support was provided by Simon Wigfield, PhD (Aspire Scientific Ltd, UK), and was funded by Gilead Sciences, Inc.

G-CAG, Global Community Advisory Group; PI, principal investigator; PrEP, pre-exposure prophylaxis.

Summary

What is your main question?

- Youth (aged 15-24) account for approximately 28% of the 1.3 million new HIV infections each year
- Does twice-yearly SC LEN work for HIV prevention (PrEP) in participants aged 16-25 years (youth) from PURPOSE 1 and PURPOSE 2?

What did you find?

- Twice-yearly SC LEN showed high efficacy and favorable safety in youth, with no clinically relevant differences in PK between youth and adults

Why is it important?

- To understand the potential of LEN to address challenges with daily oral PrEP and help reduce new HIV infections in youth, who are disproportionately affected by HIV

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LEN, lenacapavir; PK, pharmacokinetics; PrEP, pre-exposure prophylaxis; SC, subcutaneous.

Youth Account for a Significant Number of New HIV Infections Globally

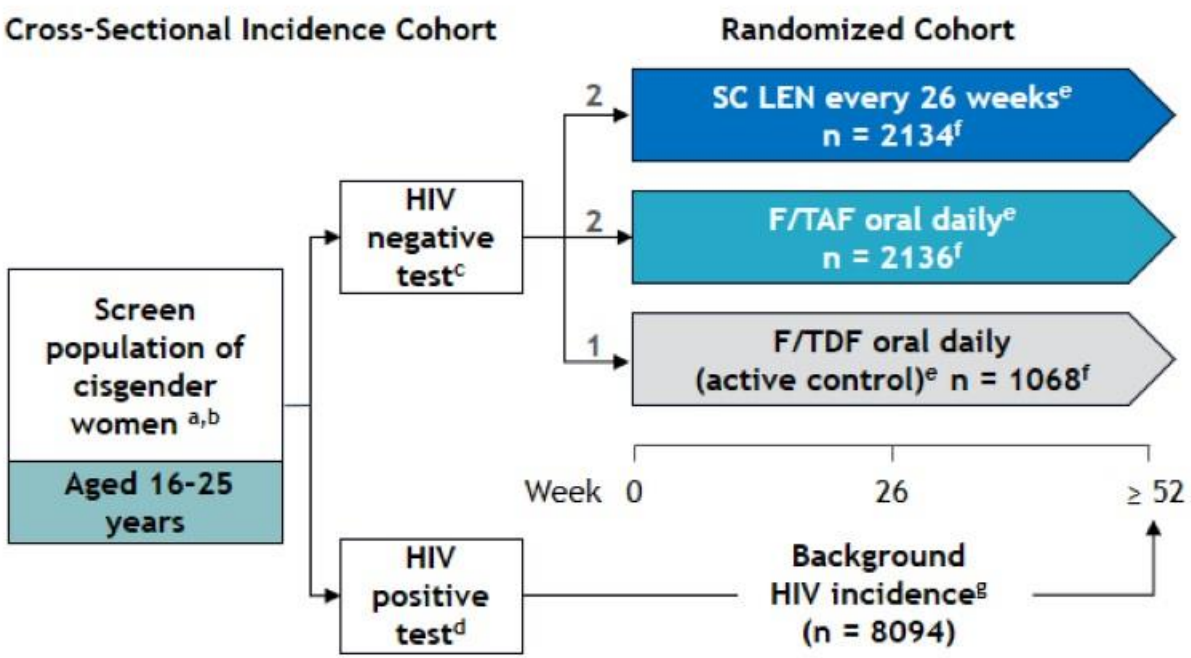
- **Youth (aged 15-24)** account for approximately **28%** of the **1.3 million new HIV infections** annually,[1] and experience unique challenges with uptake of, adherence to, and persistence on daily oral HIV PrEP[2-5]
- **LEN** is a **first-in-class**, multistage HIV-1 capsid inhibitor with **high potency** and a **long half-life**[6,7]
- **Twice-yearly SC LEN** was shown to be **efficacious, safe**, and **well-tolerated** for **HIV prevention** in highly diverse populations[8,9]

We evaluated the efficacy, safety, and PK of twice-yearly SC LEN in participants aged 16-25 years (youth) from PURPOSE 1 and PURPOSE 2

LEN, lenacapavir; PK, pharmacokinetics; PrEP, pre-exposure prophylaxis; SC, subcutaneous. 1. Joint United Nations Programme on HIV/AIDS. https://aidsinfo.unaids.org (accessed May 16, 2025). 2. Wood S, et al. *AIDS Behav*. 2019;23:2719-29. 3. Warzywoda S, et al. *Ther Adv Infect Dis*. 2024;11:1-25. 4. Muhumuza R, et al. *Arch Sex Behav*. 2021;50:1729-42. 5. Admassu M, et al. *BMC Womens Health*. 2024;24:665. 6. Segal-Maurer S, et al. *N Engl J Med*. 2022;386:1793-803. 7. Link JO, et al. *Nature*. 2020;584:614-8. 8. Bekker L-G, et al. *N Engl J Med*. 2024;391:1179-92. 9. Kelley CF, et al. *N Engl J Med*. 2025;392:1261-76.

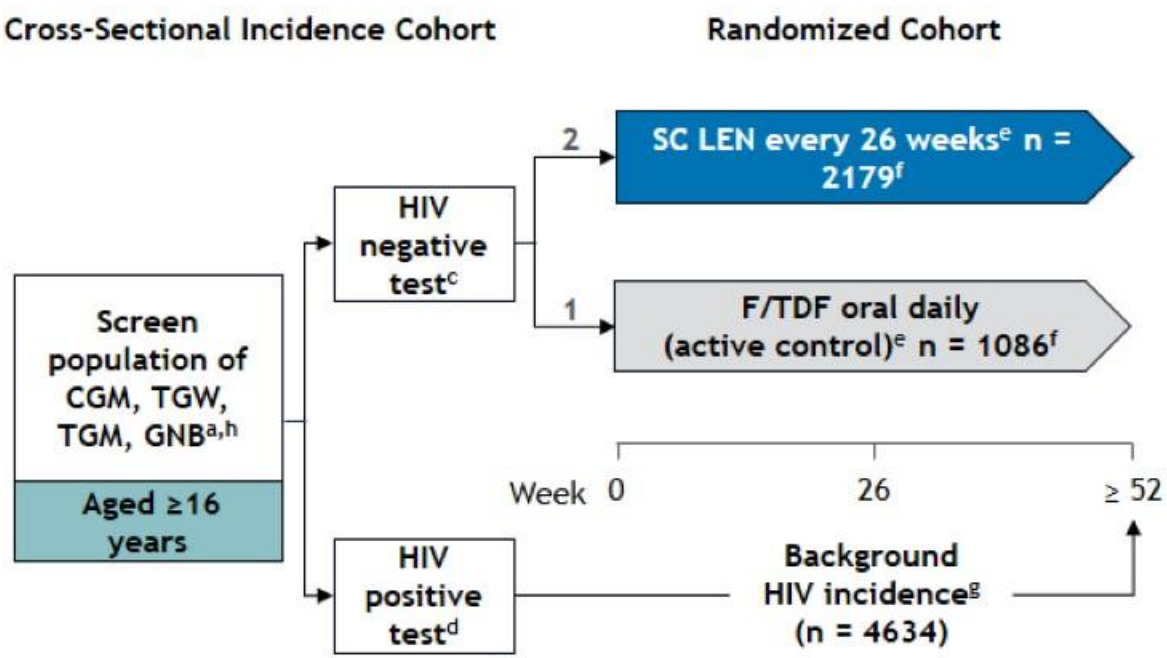
PURPOSE 1 and 2 Study Designs

PURPOSE 1



ClinicalTrials.gov: NCT04994509

PURPOSE 2



ClinicalTrials.gov: NCT04925752

[a]Not receiving PrEP and without HIV testing in past 3 months; [b]The first participant was screened in August 2021, the 50th percentile participant was randomized in May 2023, and the last participant was randomized in September 2023; [c]Participants also met eligibility criteria (including weight ≥ 35 kg, eGFR ≥ 60 mL/min, not pregnant); [d]Recency assay data were used to estimate background HIV incidence (persons testing HIV positive were referred to HIV care); [e]Plus the alternative SC/oral placebo; [f]n numbers represent the full analysis set for efficacy analyses; [g]Background HIV incidence is the incidence expected without PrEP that would have been expected in a placebo group (the counterfactual HIV incidence); [h]The first participant was screened in June 2021, the 50th percentile participant was randomized in August 2023, and the last participant was randomized in December 2023. CGM, cisgender men; eGFR, estimated glomerular filtration rate; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; GNB, gender-nonbinary; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; SC, subcutaneous; TGM, transgender men; TGW, transgender women.

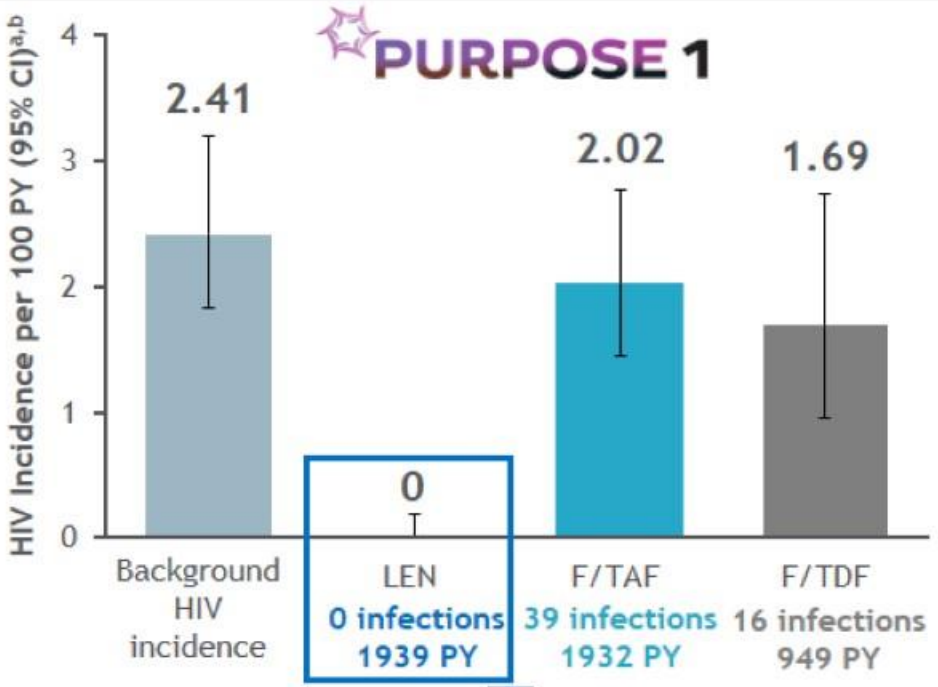
Baseline Demographics

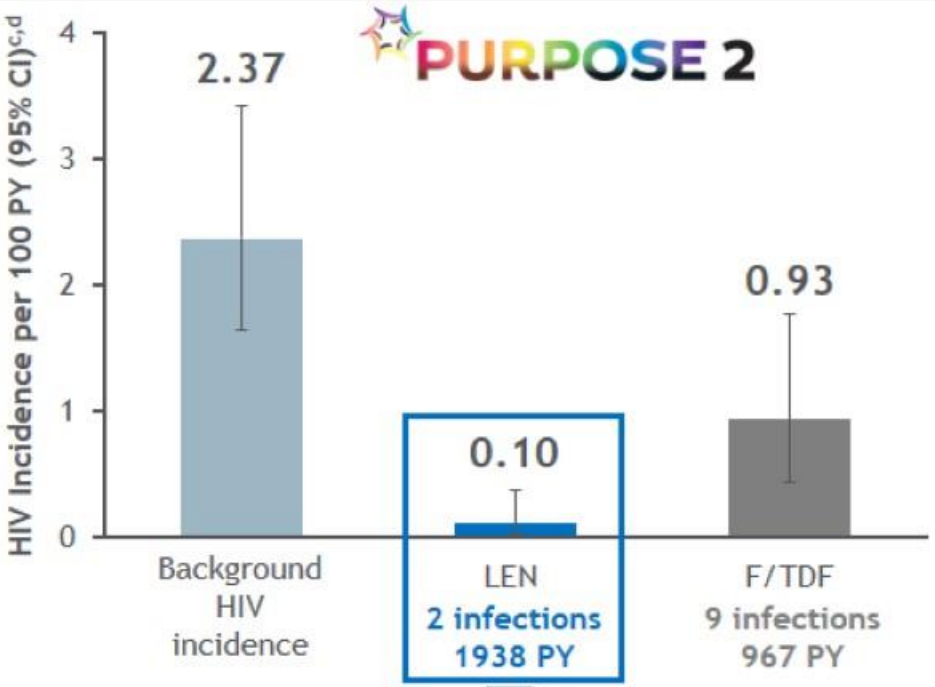
Characteristic	PURPOSE 1 (16-25 years)		PURPOSE 2 (≥ 16 years)	
	< 18 years LEN, n = 56	≥ 18 years LEN, n = 2084	≤ 25 years LEN, n = 752	> 25 years LEN, n = 1431
Median age, years (range)	17 (16-17)	21 (18-25)	22 (17-25)	32 (26-74)
16 to < 18 years, n (%)	56 (100)	0	3 (0.4)	0
≥ 18 years, n (%)	0	2084 (100)	749 (99.6)	1431 (100)
Race or ethnic group, n (%)[a]				
Asian	0	0	93 (12.4)	176 (12.4)
Black[b]	56 (100)	2081 (99.9)	315 (41.9)	496 (34.9)
Indigenous or Indigenous Ancestry[c]	0	0	199 (26.5)	142 (10.0)
White	0	0	134 (17.8)	588 (41.3)
Other and Other Multiracial[d]	0	3 (0.1)	11 (1.5)	21 (1.5)
Hispanic or Latine	0	0	423 (56.3)	955 (66.8)[e]
Median body mass index, Kg/m^2 (range)	22.5 (16.6-52.0)	25.0 (15.0-62.7)	22.7 (13.7-59.7)	26.2 (15.4-89.6)
Some college or university degree, n (%)[f]	0	184 (8.8)	258 (34.3)	847 (59.2)

PURPOSE 1 and 2 were the most racially, ethnically, age-, gender-, and geographically diverse PrEP pivotal trials

[a]Race data were unavailable for eight participants in the LEN group (> 25 years) from PURPOSE 2. [b]Black included all participants who identified as Black or of Black ancestry: 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 Alaskan Native, Black/Asian, and Black/Native Hawaiian or Pacific Islander. [c]American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, Asian/Native Hawaiian or Pacific Islander, White/Native Hawaiian or Pacific Islander, and White/American Indian or Alaskan Native. [d]Other and other multiracial included: Asian/White, Colored (South Africa), Pardo (Brazil), White/Brown (Brazil), multiracial any other, and not multiracial other. [e]Ethnicity data not available for one participant in the LEN group (> 25 years) from PURPOSE 2. [f]Highest education data were unavailable for two participants in the LEN group (≥ 18 years) from PURPOSE 1, and one participant in the LEN group (> 25 years) from PURPOSE 2. LEN, lenacapavir; PrEP, pre-exposure prophylaxis.

Only Two HIV Infections in Youth on LEN From PURPOSE 1 and 2





Overall trial population

Youth

In PURPOSE 1, zero HIV infections occurred in youth on LEN

In PURPOSE 2, two HIV infections occurred in youth on LEN

LEN demonstrated efficacy for HIV prevention in youth[1,2]

[a]Overall n: background HIV incidence group, 8094; LEN, 2134; F/TAF, 2136; F/TDF, 1068. [b]95% CIs: background HIV incidence group, 1.82-3.19; LEN, 0-0.19; F/TAF, 1.44-2.76; F/TDF, 0.96-2.74. [c]Overall n: background HIV incidence group, 4634; LEN, 2179; F/TDF, 1086.
[d]95% CIs: background HIV incidence group, 1.65-3.42; LEN, 0.01-0.37; F/TDF, 0.43-1.77.
CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; PY, person-years.

1. Bekker L-G, et al. *N Engl J Med*. 2024;391:1179-92. 2. Kelley CF, et al. *N Engl J Med*. 2025;392:1261-76.

LEN Was Safe and Well Tolerated in Youth

Adverse events, n (%)[a,b,c]	PURPOSE 1 (16-25 years)		PURPOSE 2 (≥ 16 years)	
	< 18 years LEN, n = 56	≥ 18 years LEN, n = 2084	≤ 25 years LEN, n = 752	> 25 years LEN, n = 1431
Any adverse events	41 (73.2)	1590 (76.3)	537 (71.4)	1070 (74.8)
Grade ≥ 2	19 (33.9)	1092 (52.4)	403 (53.6)	770 (53.8)
Grade ≥ 3	4 (7.1)	84 (4.0)	28 (3.7)	63 (4.4)
Serious adverse events	1 (1.8)	58 (2.8)	22 (2.9)	49 (3.4)
Adverse events related to study drug	9 (16.1)	489 (23.5)	79 (10.5)	184 (12.9)
Adverse events leading to discontinuation of study drug	0	5 (0.2)	5 (0.7)	2 (0.1)
Laboratory abnormalities, n with ≥ 1 post-baseline result	55	2073	739	1414
Any grade	49 (89.1)	1881 (90.7)	597 (80.8)	1225 (86.6)
Grade 3	6 (10.9)	90 (4.3)	39 (5.3)	145 (10.3)
Grade 4	0	20 (1.0)	24 (3.2)	35 (2.5)

Adverse events and lab abnormalities were generally similar in youth receiving LEN in PURPOSE 1 and 2

[a]Adverse events are treatment emergent in participants who received at least one dose of study drug; adverse events coded according to the Medical Dictionary for Regulatory Activities, Version 27.0. [b]Excludes injection-site reactions to SC LEN. [c]Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric adverse events, Version 2.1.
LEN, lenacapavir; SC, subcutaneous.

LEN Was Safe and Well Tolerated in Youth

Adverse events occurring in ≥ 5% of participants, n (%)[a,b,c]	PURPOSE 1 (16-25 years)	
	< 18 years LEN, n = 56	≥ 18 years LEN, n = 2084
Headache	9 (16.1)	276 (13.2)
Genitourinary chlamydia infection	7 (12.5)	293 (14.1)
Genitourinary tract gonococcal infection	5 (8.9)	136 (6.5)
Diarrhea	4 (7.1)	129 (6.2)
Dizziness	4 (7.1)	116 (5.6)
Gynecological chlamydia infection	4 (7.1)	22 (1.1)
Vomiting	3 (5.4)	122 (5.9)
Anemia	3 (5.4)	45 (2.2)
Upper respiratory tract infection	2 (3.6)	269 (12.9)
Urinary tract infection	1 (1.8)	306 (14.7)
Vaginal discharge	1 (1.8)	165 (7.9)
Vulvovaginal candidiasis	1 (1.8)	145 (7.0)
Nausea	0	144 (6.9)

Adverse events occurring in ≥ 5% of participants, n (%)[a,b,c]	PURPOSE 2 (≥ 16 years)	
	≤ 25 years LEN, n = 752	> 25 years LEN, n = 1431
Anal chlamydia infection	118 (15.7)	171 (11.9)
Anal gonococcal infection	114 (15.2)	119 (8.3)
Oropharyngeal gonococcal infection	109 (14.5)	174 (12.2)
Upper respiratory tract infection	48 (6.4)	100 (7.0)
Nausea	42 (5.6)	47 (3.3)
Latent syphilis	41 (5.5)	73 (5.1)
Influenza	37 (4.9)	83 (5.8)
Headache	36 (4.8)	83 (5.8)
Diarrhea	34 (4.5)	112 (7.8)

Adverse events in youth were consistent with prior LEN studies and with conditions commonly observed in the PURPOSE 1 and PURPOSE 2 study populations

[a]Adverse events are treatment emergent in participants who received at least one dose of study drug; adverse events coded according to the Medical Dictionary for Regulatory Activities, Version 27.0. [b]Excludes injection-site reactions to SC LEN.
[c]Adverse events sorted by descending order in the LEN group (< 18 years) for PURPOSE 1 and the LEN group (≤ 25 years) for PURPOSE 2.
LEN, lenacapavir; SC, subcutaneous.

Injection-Site Reactions with LEN

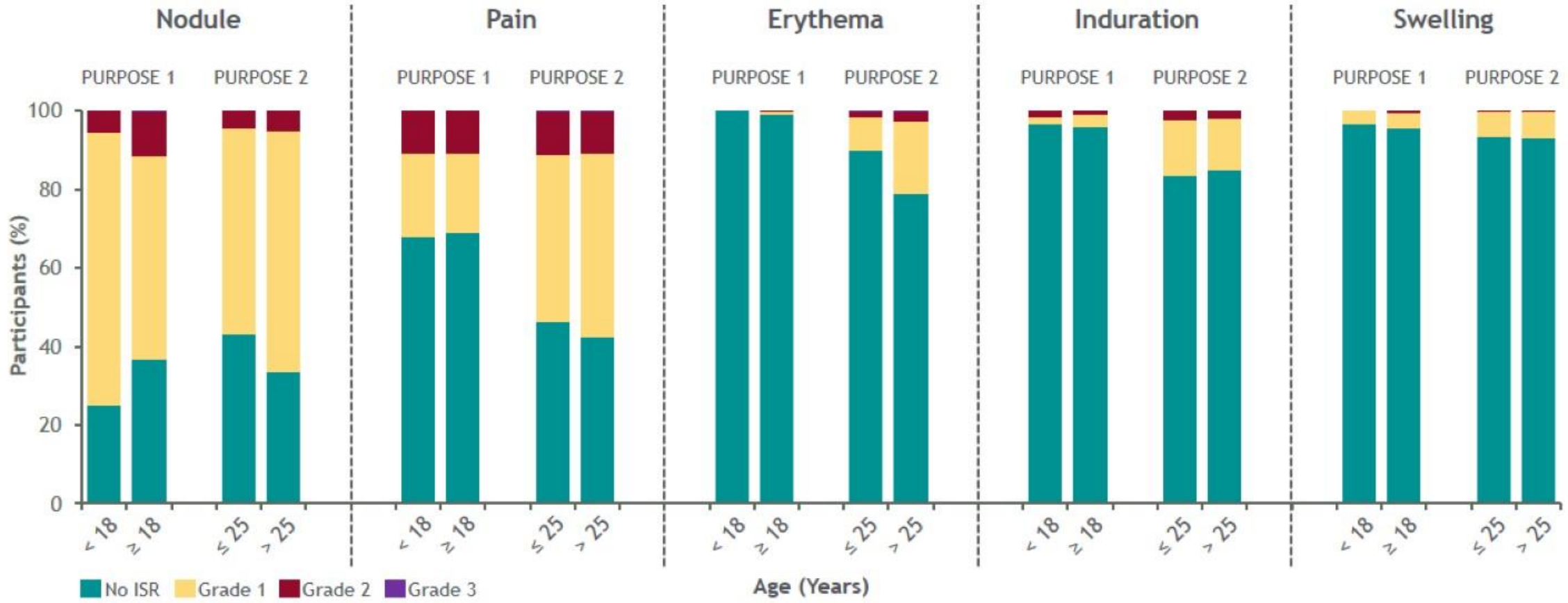
Injection-site reactions, n (%)[a]	PURPOSE 1 (16-25 years)		PURPOSE 2 (≥ 16 years)	
	< 18 years LEN, n = 56	≥ 18 years LEN, n = 2084	≤ 25 years LEN, n = 752	> 25 years LEN, n = 1431
Participants who received >1 injection, n	56	2084	752	1431
Any grade injection-site reactions	44 (78.6)	1428 (68.5)	619 (82.3)	1197 (83.6)
Grade 1	35 (62.5)	1027 (49.3)	485 (64.5)	956 (66.8)
Grade 2	9 (16.1)	397 (19.0)	130 (17.3)	231 (16.1)
Grade 3	0	4 (0.2)	4 (0.5)	10 (0.7)
Serious injection-site reactions	0	0	0	0
Injection-site reactions leading to discontinuation of the study drug	0	4 (0.2)	7 (0.9)	19 (1.3)

Injection-site reactions in youth were mostly low grade and consistent with those reported in the PURPOSE 1 and 2 study populations[1,2]

[a]Injection-site reactions that are reported here were to study drug-related injection only and were coded according to the Medical Dictionary for Regulatory Activities, Version 27.0.
LEN, lenacapavir.

1. Bekker L-G, et al. *N Engl J Med*. 2024;391:1179-92. 2. Kelley CF, et al. *N Engl J Med*. 2025;392:1261-76.

Injection-Site Reactions with LEN



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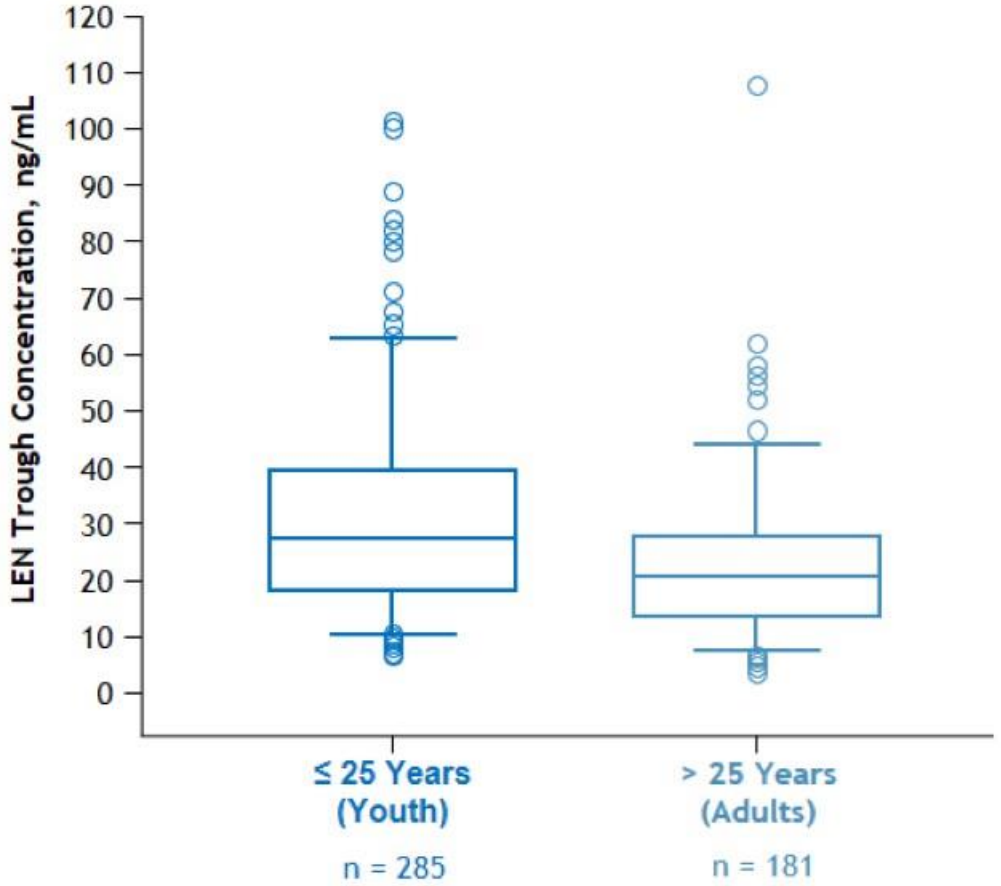
LEN[a] Plasma Concentrations at Week 26 (C_{trough}) in the Randomized Blinded Phase in PURPOSE 1 and 2 (Youth vs Adults)[b]



Observed LEN plasma concentrations were generally comparable between youths and adults

Participants who became pregnant, received oral LEN bridging, or were diagnosed with HIV-1 were excluded. LEN plasma concentrations were from a randomly preselected 10% of participants.
Box = Q1 and Q3; horizonal line inside box = median; whiskers = 5th and 95th percentiles. Values below the limit of quantification were treated as zero.
[a]LEN administered as subcutaneous injection of 927 mg. [b]Category for ≤ 25 years includes PURPOSE 1 and 2 participants; category for > 25 years includes only PURPOSE 2 participants.
C_{trough}, trough concentration; LEN, lenacapavir; Q1, first quartile; Q3, third quartile.

Conclusions

- In this study, we described the results of a combined PURPOSE 1 and 2 analysis in youth receiving SC LEN
- Two HIV seroconversions (in PURPOSE 2) were observed among youth receiving LEN
- LEN was safe and well tolerated in youth
- LEN PK levels in youth were generally comparable with those in adults
  - This supports extrapolation of efficacy in youth

Twice-yearly SC LEN had high efficacy, favorable safety, and no clinically relevant PK differences in youth, supporting the potential of LEN to address challenges with daily oral PrEP and help reduce new HIV infections among youth

LEN, lenacapavir; **PK**, pharmacokinetic; **PrEP**, pre-exposure prophylaxis; **SC**, subcutaneous.

Acknowledgments

We extend our gratitude to the PURPOSE trial participants and their communities, our Global Community Advisory and Accountability Groups, the site staff and investigators, and all the members of the PURPOSE study teams

PURPOSE 1 Study Team

Quarraisha Abdool Karim, Khatija Ahmed, Dos Santos Ankomisyani, Joanne Batting, Johanna Alida Baumgarten, Trevor Beattie, Ngundu Behuhuma, Linda-Gail Bekker, Mags Beksinska, Gabriella Benade, William Brumskine, Sithandiwe Buthelezi, Valma Craffert, Alicia Catherine Desmond, Nkosilathi Dlodlo, Nokuphiwa Doncabe, Linamandla Douglas, Phillip du Preez, Megan Easton, Carla Edeling, Vinodh Aroon Edward, Lindsey Faul, Katherine Gill, Nicole Glover, Thasha Gounden, Vaneshree Govender, Nicole Gracie, Willem Hanekom, Ishana Harkoo, Chiara Ilett, Manjeetha Jaggernath, Nitesha Jeenarain, Lindsay Jeffrey, Alex Jemba, Samuel Kabwigu, Edrine Kalule, Priya Kassim, Lindsay Kew, Reolebogile Kgoa, Johara Khan, Mlungisi Khanyile, Zainab Kharva, Noluthando Khiya, Khensani Khoza, Godfrey Kigozi, Ronald Kisitu, Noah Kiwanuka, Carla Kloppers, Philip Kotze, Limakatso Lebina, Cheryl E Louw, Mmatshepho Maditsi, Philisiwe Makhoba, Heeran Makkan, Morakane Alicia Caroline Makwela, Moelo Malahleha, Mookho Malahleha, Malebo Mampane, Mmatsie Manentsa, Leila Mansoor, Flavia Matovu Kiweewa, Valerie Mlotshwa, Mbalizethu Mntambo, Rorisang Mofokeng, Dhayendre Moodley, Mgcini Moyo, Timothy Muwonge, Vimla Naicker, Kavith Naidoo, Logashvari Naidoo, Megeshinee Naidoo, Gonasagri Nair, Joan Nakakande, Gertrude Nakigozi, Fred Nalugoda, Joyce Namale Matovu, Anusha Nana, Esther Nantambi, Terusha Navsaria, Nkosiphile Ndlovu, Theodorah Ndzhukule, Tanya Nielson, Nomfundo Ntuli, Thesla Palanee-Phillips, Ravindre Panchia, Menoka Pillay, Saresha Pillay, Disebo Potloane, Sunai Ramdhani, Caro-Lee Saal, Khanyile Saleni, Ni Ni Sein, Pearl Selepe, Melissa Senne, Nishanta Singh, Yashna Singh, Jennifer Smit, Elizabeth Spooner, Ali Ssetaala, Nicola Thomas, Andrew Tlagadi, Mishka Valjee, Amy M Ward, Ben Wasswa, Zinhle Ayanda Zwane, Zwelethu Zwane.

PURPOSE 2 Study Team

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Accelerating Access for Global HIV Prevention

Expansive licensing	Rapid technology transfer	Simultaneous submissions
Earliest and geographically broadest (120 countries) voluntary licensing strategy ever for an antiretroviral	Agreements with 6 generics & full technology transfer within 3 months; Global Fund 2 million people for 3 years	US Approval June 2025 EU, EUM4All, South Africa, Brazil, Canada, Australia, Switzerland & more coming
Expediting Regulatory Review	**WHO endorsement**	**Manufacturing readiness**
EU-M4all application enables faster reviews in low- and middle-income countries	Guidelines released July 14, 2025 & prequalification later this year will facilitate global adoption	Gilead-supplied no-profit product & partnership agreements, bridging to sustainable generic supply

Collaborative implementation science studies to inform sustainable access, eg South Africa (Project PrEP, UNITAID/Wits RHI; ALIGN, Gates Foundation/Desmond Tutu Health Foundation) and Brazil (ImPrEP, IUNITAID/Fiocruz)