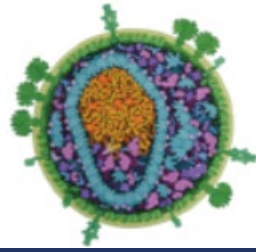


# Pharmacokinetics and Safety of Once-Yearly Lenacapavir

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32nd Conference on Retroviruses and Opportunistic Infections (CROI); March 9-12, 2025; San Francisco, CA, USA

# Disclosures

- All authors are employees of Gilead Sciences, Inc., Foster City, CA, USA
- Gilead Sciences funded and designed the study, monitored the conduct of the trial, received the data, and performed analyses
- Medical writing support was provided by Jenna Steere, PhD, of Aspire Scientific Ltd (Bollington, UK), and was funded by Gilead Sciences, Inc.

# Background and Objectives

- Lenacapavir (LEN) is a long-acting potent capsid inhibitor[1,2]
- Administered as twice-yearly SC injections, LEN demonstrated efficacy and safety for HIV PrEP in diverse populations in two Phase 3 trials: PURPOSE 1 (NCT04994509) and PURPOSE 2 (NCT04925752)[3,4]
- Once-yearly LEN administration could further address HIV PrEP barriers, such as stigma, adherence challenges, and the need for frequent healthcare interactions,[5,6] by providing an additional option to people who want or need PrEP
- When injected, LEN forms a drug depot and is slowly released from the site of administration, leading to its long-acting PK[1,2]
- We evaluated two novel once-yearly IM LEN formulations with the aim of achieving similar concentrations to twice-yearly SC LEN

**This analysis assessed the PK and safety of two different once-yearly LEN formulations**

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

1. Link JO, et al. *Nature*. 2020;584:614-8. 2. Hadas D-S, et al. *Curr Opin HIV AIDS*. 2022;17:15-21. 3. Bekker LG. *N Engl J Med*. 2024;391:1179-92. 4. Kelley CF, et al. *N Engl J Med*. Published online November 27, 2024. doi:10.1056/NEJMoa2411858. 5. Miller AS, et al. *J Urban Health*. 2023;100:212-4. 6. Rogers BG, et al. *BMC Public Health*. 2023;23:1643.

# Study Design

## Open-label, Phase 1 study evaluating the PK, safety, and tolerability of a single 5000 mg[a] IM dose of two free-acid LEN formulations: Formulations 1 and 2

**Cohort 1: Formulation 1 (5% EtOH; n = 20)**

**Cohort 2: Formulation 2[b] (10% EtOH; n = 20)**

### Study Population

- Healthy participants with a low likelihood of HIV acquisition
- Aged 18–55 years
- BMI ≤ 35.0 kg/m$^2$


- Clinic inpatient observation
- ▲ Study drug dosing: two 5-mL IM gluteal injections
- × Intensive PK sample (≤ 5 minutes before dose, and 2, 4, 8,12, 24 and 36 hours post dose)
- \+ Single anytime PK sample[c] follow-up: Days 22-43 (± 1 day), Days 57-141 (± 3 days), Days 169-393 (± 5 days)

### Safety Assessments

- Laboratory evaluation
- Investigator-reported AEs
- Participant-reported outcomes including pain measures on a qualitative scale

### PK Analysis/Outcomes

- PK ($AUC_{Days\ 1\text{-}365}$, $C_{max}$, $T_{max}$, and $C_{trough}$)
- Compared LEN concentrations between once-yearly IM and twice-yearly SC LEN

[a] 2 × 5 mL of 500 mg/mL. [b]Half of participants who received Formulation 2 were pretreated for approximately 10 minutes with an ice pack at the site of injection. [c]A single anytime PK sample was collected on Days 3, 4, 6, 8, 10, 15, 22, 29, 36, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 351, 365, 379, and 393, and at the early termination visit (if applicable).

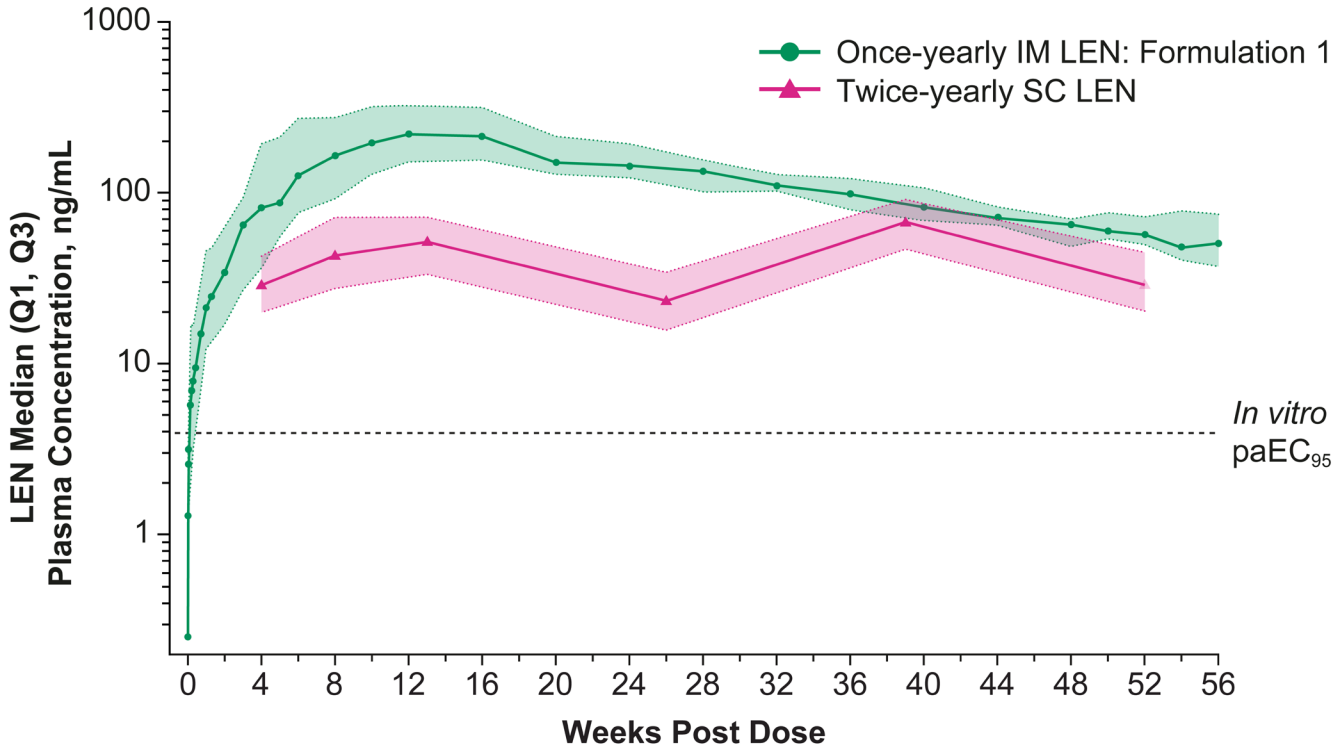
**AE**, adverse event; **AUC**, area under the concentration-time curve; **$AUC_{Days\ 1\text{-}365}$**, area under the concentration-time curve for the once-yearly dosing interval calculated from days 1-365; **BMI**, body mass index; **$C_{max}$**, observed peak plasma concentration; **$C_{trough}$**, estimated trough concentration at the end of 364 days; **EtOH**, ethanol; **IM**, intramuscular; **LEN**, lenacapavir; **PK**, pharmacokinetic; **$T_{max}$**, time to reach peak plasma concentration.

# Participant Demographics

| | LEN Formulation 1<br>n = 20 | LEN Formulation 2<br>n = 20 |
|---|---|---|
| **Age, years (Q1, Q3)** | **37 (29, 50)** | **33 (29, 45)** |
| **Assigned male sex at birth, n (%)** | **13 (65)** | **13 (65)** |
| **Assigned female sex at birth, n (%)** | **7 (35)** | **7 (35)** |
| **Race, n (%)** | | |
| Black or African American | **3 (15)** | **5 (25)** |
| White | **17 (85)** | **15 (75)** |
| **Ethnicity, n (%)** | | |
| Hispanic or Latine | **20 (100)** | **16 (80)** |
| Not Hispanic or Latine | **0** | **4 (20)** |
| **Weight, kg (Q1, Q3)** | **73.6 (68.6, 86.8)** | **77.1 (72.5, 85.6)** |
| **BMI, kg/m$^2$ (Q1, Q3)** | **26.5 (24.1, 29.4)** | **28.0 (24.9, 30.0)** |

Data are n (%) or median (Q1, Q3).
**BMI**, body mass index; **LEN**, lenacapavir; **Q1**, first quartile; **Q3**, third quartile.

# Once-yearly IM Formulation 1 Compared With Twice-yearly SC LEN

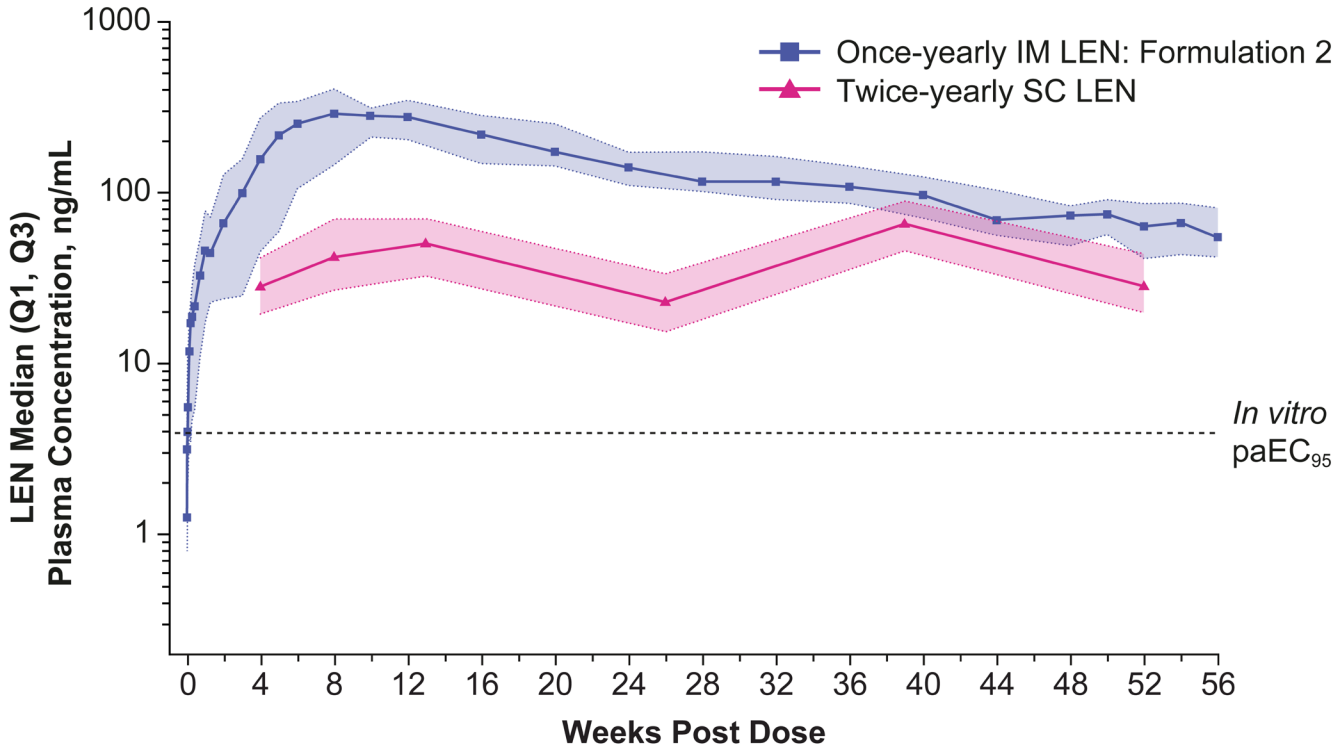



| PK Parameter, median (Q1, Q3) | LEN Formulation 1 (n = 20)<br>5000 mg<br>(2 × 5 mL of 500 mg/mL with 5% EtOH) |
|---|---|
| $C_{max}$, ng/mL | 247 (184, 346) |
| $T_{max}$, days | 84.1 (56.1, 112) |
| $AUC_{Days\ 1\text{-}365}$, h*µg/mL | 1011 (881, 1490) |
| $C_{trough\ (Day\ 365)}$, ng/mL | 57.0 (49.9, 72.4) |

**Concentrations with once-yearly IM LEN were higher than twice-yearly SC LEN for 56 weeks**

Horizontal dashed line at 3.87 ng/mL represents *in vitro* $paEC_{95}$. SC LEN 927 mg on Day 1 and at the end of 26 weeks, with oral LEN 600 mg on Days 1 and 2, in PURPOSE 1 and PURPOSE 2. PK parameters; n = 15 ($C_{max}$ and $T_{max}$) and n = 13 ($AUC_{Ddys\ 1\text{-}365}$ and $C_{trough}$).
**AUC**, area under the concentration-time curve, $AUC_{Days\ 1\text{-}365}$, AUC for the once-yearly dosing interval calculated from Days 1-365; $C_{max}$, peak plasma concentration; $C_{trough\ (Day\ 365)}$, trough concentration at Day 365; **EtOH**, ethanol; **IM**, intramuscular; **LEN**, lenacapavir; $paEC_{95}$, protein-adjusted 95% effective trough concentration; **PK**, pharmacokinetics; **Q1**, first quartile; **Q3**, third quartile, **SC**, subcutaneous; $T_{max}$, time to reach peak plasma concentration

# Once-yearly IM Formulation 2 Compared With Twice-yearly SC LEN




| PK Parameter, median (Q1, Q3) | LEN Formulation 2 (n = 20)<br>5000 mg<br>(2 × 5 mL of 500 mg/mL with 10% EtOH) |
|---|---|
| $C_{max}$, ng/mL | 336 (234, 474) |
| $T_{max}$, days | 69.9 (55.3, 105) |
| $AUC_{Days\ 1\text{-}365}$, h*µg/mL | 1274 (1177, 1705) |
| $C_{trough\ (Day\ 365)}$, ng/mL | 65.6 (41.8, 87.1) |

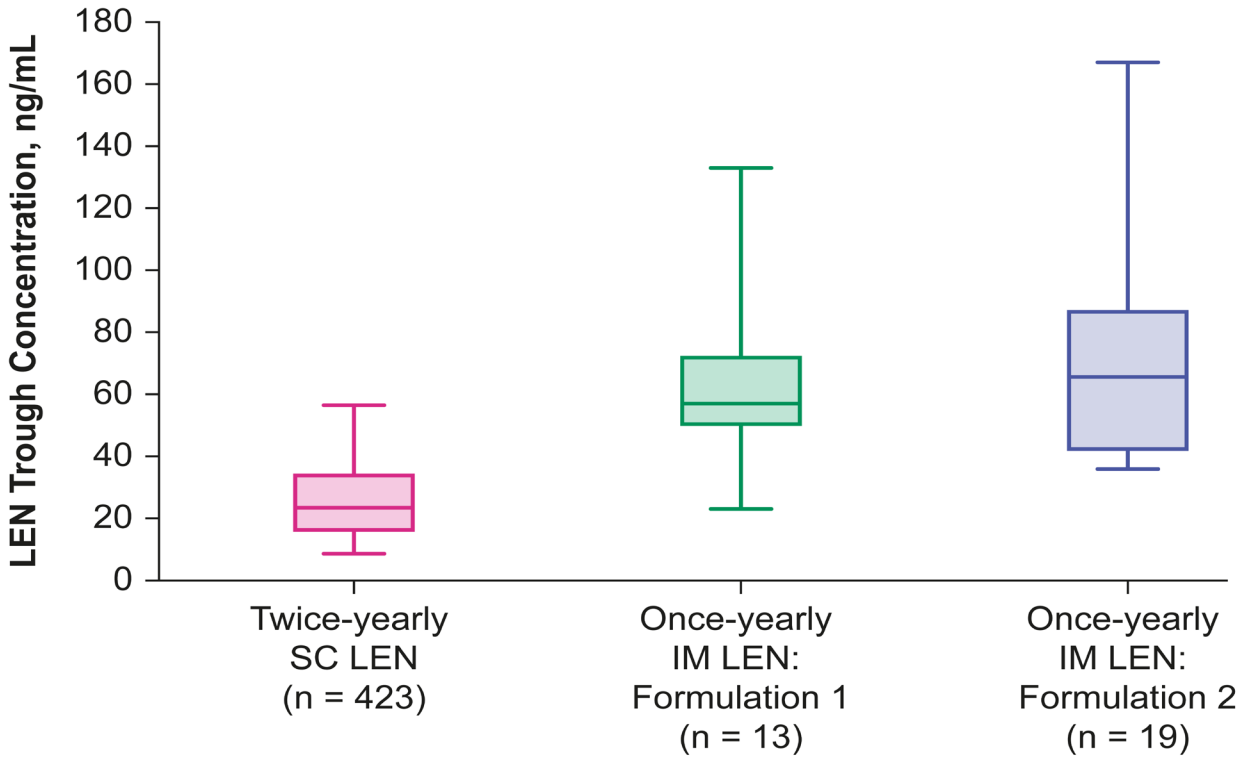
$C_{max}$ was at least 3-fold lower than LEN concentrations previously studied without safety concerns[1]

**Concentrations with once-yearly IM LEN were higher than twice-yearly SC LEN for 56 weeks**

Horizontal dashed line at 3.87 ng/mL represents *in vitro* $paEC_{95}$. SC LEN 927 mg on Day 1 and at the end of 26 weeks, with oral LEN 600 mg on Days 1 and 2, in PURPOSE 1 and PURPOSE 2. PK parameters; n = 15 ($C_{max}$ and $T_{max}$) and n = 19 ($AUC_{Days\ 1\text{-}365}$ and $C_{trough}$).
**AUC**, area under the concentration-time curve; $AUC_{Days\ 1\text{-}365}$, AUC for the once-yearly dosing interval calculated from Days 1-365; $C_{max}$, peak plasma concentration; $C_{trough\ (Day\ 365)}$, trough concentration at Day 365; **EtOH**, ethanol; **IM**, intramuscular; **LEN**, lenacapavir; $paEC_{95}$, protein-adjusted 95% effective trough concentration; **PK**, pharmacokinetics; **Q1**, first quartile; **Q3**, third quartile; **SC**, subcutaneous; $T_{max}$, time to reach peak plasma concentration.

1. Jogiraju V, et al. *Antimicrob Agents Chemother*. 2024;68:e0134423.

# Comparison of $C_{trough}$ Between Once-Yearly IM Formulations and Twice-Yearly SC LEN




| Formulation | Median $C_{trough}$, ng/mL (Q1, Q3) |
|---|---|
| Twice-yearly SC LEN (week 26) | 23.4 (15.7, 34.3) |
| Once-yearly IM LEN: Formulation 1 (week 52) | 57.0 (49.9, 72.4) |
| Once-yearly IM LEN: Formulation 2 (week 52) | 65.6 (41.8, 87.1) |

**Concentrations for all participants following once-yearly IM LEN formulations were similar to or higher than those for the twice-yearly SC LEN that demonstrated efficacy in PURPOSE 1 and 2**

[a]Boxes represent the interquartile range (25th and 75th percentiles) with solid lines in the middle representing the median and "whiskers" representing 5th and 95th percentiles.
$C_{trough}$, trough concentration; **IM**, intramuscular; **LEN**, lenacapavir; **SC**, subcutaneous.

# Both Formulations of LEN Were Safe and Well Tolerated

| Safety Parameter, n (%) | LEN Formulation 1 n = 20 | LEN Formulation 2 n = 20 |
|---|---|---|
| **Any AE** | 18 (90) | 16 (80) |
| **AEs occurring in ≥ 10% of participants in a cohort** | | |
| Diarrhea | 2 (10) | 0 |
| Injection-site pain | 16 (80) | 15 (75) |
| Injection-site bruising | 2 (10) | 1 (5) |
| Injection-site swelling | 4 (20) | 0 |
| Pain with ambulation | 0 | 4 (20)[a] |
| Feeling hot | 0 | 2 (10) |
| Headache | 0 | 5 (25) |
| Dizziness | 0 | 2 (10) |
| **Study drug-related AEs**[b] | 17 (85) | 16 (80) |
| **Any Grade ≥ 3 AEs**[b] | 0 | 2 (10) |
| **Study drug-related Grade ≥ 3 AEs**[b] | 0 | 1 (5)[c] |
| **Any serious AEs**[b] | 0 | 1 (5) |
| **Study drug-related serious AEs**[b] | 0 | 0 |
| **Death** | 0 | 0 |
| **Grade ≥ 3 laboratory abnormalities** | 6 (30)[d] | 3 (15)[e] |

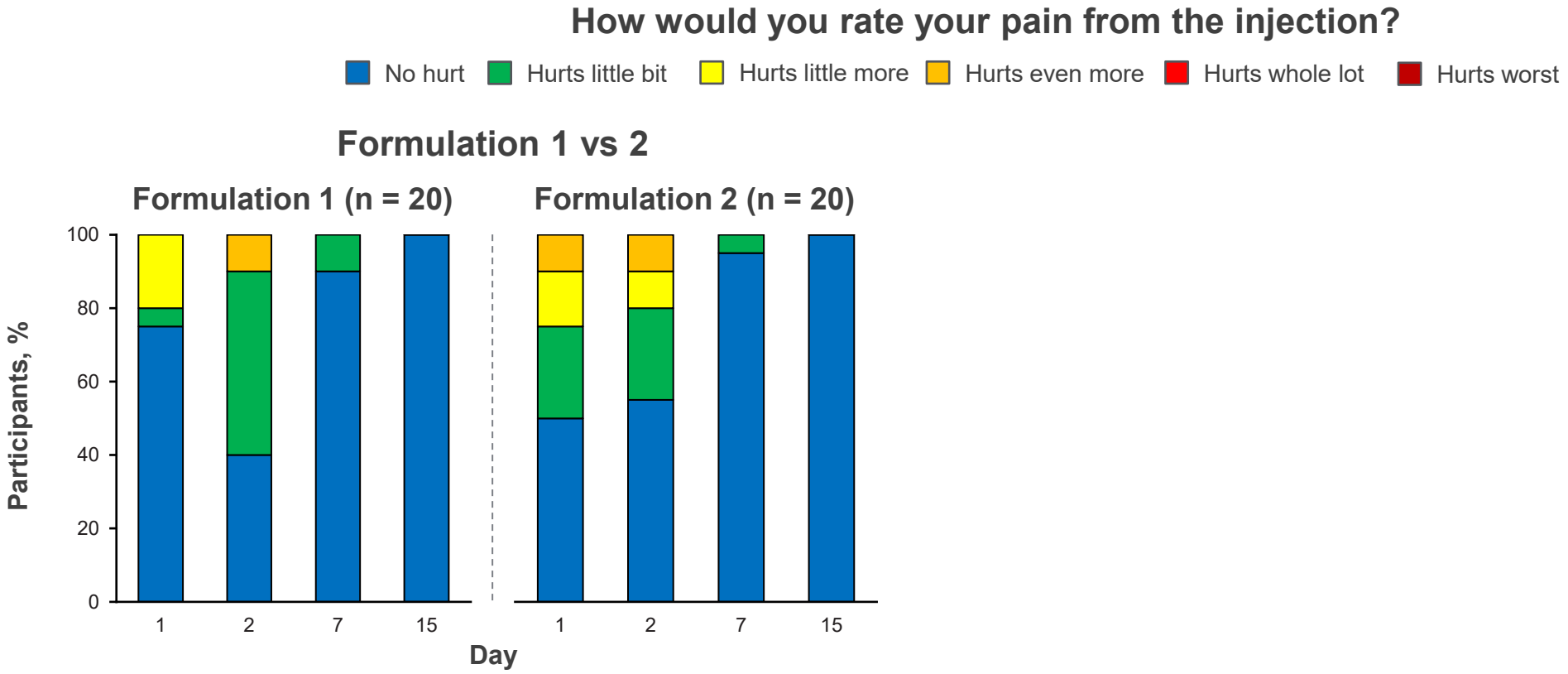
**Most adverse events were mild or moderate; no Grade 4 adverse events or laboratory abnormalities**

[a]Reported as gait disturbance by the investigator and defined as difficulty walking due to pain at the injection site but did not appear to limit daily activities. [b]Whether or not TEAEs were deemed to be related to study drug was determined by the study investigator.
[c]One participant who received Formulation 2 had LEN-related Grade 3 injection-site pain and syncope. [d]n = 3 increased low-density lipoprotein; n = 1 each of increased creatinine kinase, increased lipase, hyperkalemia, increased triglycerides, glycosuria.
[e]n = 2 decreased creatinine clearance; n = 1 hypercholesterolemia; n = 1 increased low-density lipoprotein.



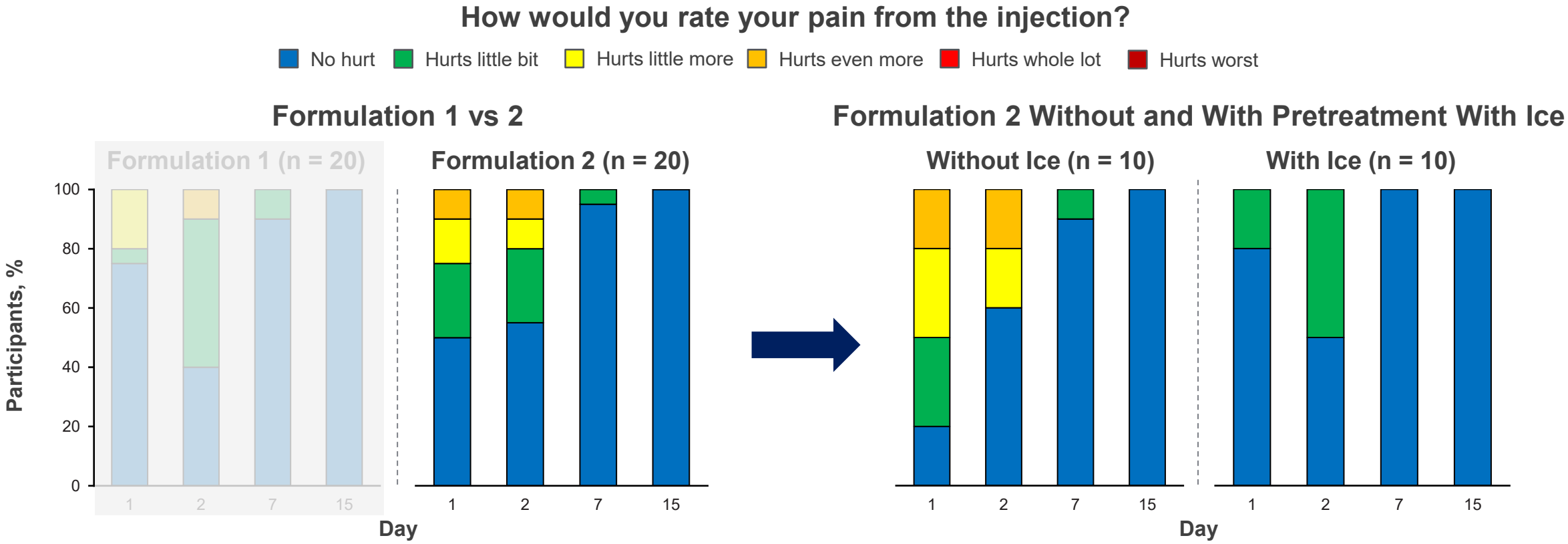
**AE**, adverse event; **LEN**, lenacapavir.

# Participant-Reported Injection-Site Pain Diminished Over Time




**Most participants reported no or mild pain, which typically resolved within 1 week**

# Participant-Reported Injection-Site Pain Decreased With Ice Pretreatment




**Most participants reported no or mild pain, which typically resolved within 1 week**
**Pretreatment with ice decreased pain ratings on Days 1 and 2 for Formulation 2**

# Conclusions

- Once-yearly intramuscular LEN maintained plasma concentrations higher than those associated with efficacy for twice-yearly subcutaneous LEN for PrEP for >12 months.
- Both formulations were safe and well tolerated
  - Injection-site pain was the most commonly reported AE- generally mild, resolved after a few days, and reduced by pretreatment with ice
- Preliminary population PK modeling results suggest that a dose lower than 5000 mg could maintain target concentrations for 1 year
- These data support the planned Phase 3 study for once-yearly IM LEN for HIV PrEP

**Once-yearly IM LEN for HIV PrEP has the potential to improve PrEP uptake and persistence and thus improve the scalability and public health impact of PrEP in populations who would benefit most**



**AE**, adverse event; **IM**, intramuscular; **LEN**, lenacapavir; **PK**, pharmacokinetics; **PrEP**, pre-exposure prophylaxis; **SC**, subcutaneous.

# Acknowledgments


- We would like to extend our thanks to all study participants for their participation
- This study was funded by Gilead Sciences, Inc.
- All authors contributed to and approved the presentation; medical writing support was provided by Jenna Steere, PhD, of Aspire Scientific (Bollington, UK), and was funded by Gilead Sciences, Inc.


- Correspondence: Renu Singh, renu.singh16@gilead.com

# Manuscript in *The Lancet* Tues Mar 11

THE LANCET

Articles

## Pharmacokinetics and safety of once-yearly lenacapavir: a phase 1, open-label study

*Vamshi Jogiraju, Pallavi Pawar, Jenna Yager, John Ling, Gong Shen, Anna Chiu, Emma Hughes, Ramesh Palaparthy, Christoph Carter, Renu Singh*

### Summary

**Background** Long-acting antiretrovirals can address barriers to HIV pre-exposure prophylaxis (PrEP), such as stigma and adherence. In two phase 3 trials, twice-yearly subcutaneous lenacapavir was safe and highly efficacious for PrEP in diverse populations. Furthering long-acting PrEP efforts, this study assessed the pharmacokinetics and safety of two once-yearly intramuscular lenacapavir formulations.

**Methods** This phase 1, open-label study in participants aged 18–55 years without HIV evaluated the pharmacokinetics, safety, and tolerability of two lenacapavir free acid formulations administered by ventrogluteal intramuscular injection as a single 5000 mg dose (formulation 1 with 5% w/w ethanol, formulation 2 with 10% w/w ethanol). Pharmacokinetic samples were collected at prespecified timepoints up to 56 weeks. Lenacapavir plasma concentrations were measured with a validated liquid chromatography–tandem mass spectrometry method and summarised with non-compartmental analysis. Pharmacokinetic parameters evaluated included the area under the concentration–time curve for the once-yearly dosing interval calculated from days 1 to 365 ($AUC_{days\ 1–365}$), peak plasma concentration, time to reach peak plasma concentration, and trough concentration ($C_{trough}$). Plasma concentration data from phase 3 studies of twice-yearly subcutaneous lenacapavir (PURPOSE 1 and PURPOSE 2) were pooled for comparison with once-yearly intramuscular lenacapavir formulations. Safety and tolerability, including participant-reported pain scores, were assessed.

**Findings** 20 participants received lenacapavir formulation 1 and 20 received lenacapavir formulation 2. For estimation of pharmacokinetic parameters, sample size varied over time with at least 13 participants (formulation 1) and at least

**Gilead Sciences, Foster City, CA, USA** (V Jogiraju PhD, P Pawar PhD, J Yager PharmD, J Ling PhD, G Shen PhD, A Chiu PhD, E Hughes PhD, R Palaparthy PhD, C Carter MD, R Singh PhD)

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# Lenacapavir for PrEP at CROI 2025




## AM

**Oral:** Lenacapavir Efficacy, Safety, and Pharmacokinetics, in Adolescents and Adults in PURPOSE 1
(Katherine Gill)
**Time:** 10:29 AM PT
**Session:** (S0-3) Maternal-Child Health and Treatment of Malignancies;
San Francisco Ballroom A

**Oral:** Pharmacokinetics and Safety of Once-Yearly Formulations of Lenacapavir
(Renu Singh)
**Time:** 10:29 AM PT
**Session:** (S0-7) Antivirals For HIV, MPXV, and SARS-CoV-2: New Drug Strategies and Resistance;
San Francisco Ballroom B

**Oral:** Adherence to F/TAF in Cisgender Women Prevents HIV with Low Risk of Resistance or Diagnostic Delay
(Flavia Matovu Kiweewa)
**Time:** 10:29 AM PT
**Session:** (S0-12) Expanding the Prevention Toolbox;
San Francisco Ballroom D

## PM

**Poster (1230):** PURPOSE 1: Preference for Twice-Yearly Injection vs Daily Oral Pills for HIV PrEP in Cisgender Women
(Leila E Mansoor)
**Time:** 2:30–4.00 PM PT
**Session:** (S-05) PrEP Implementation: Hopes, Dreams, and Aspirations

**Late Breaker Poster (1234):** Qualitative Assessment of Acceptability and Preferences for Injectable and Oral PrEP in PURPOSE 1
(Elizabeth T Montgomery)
**Time:** 2:30–4.00 PM PT
**Session:** (S-06) Innovations in PrEP Products