# Impact of Subcutaneous Administration Sites on the Clinical Pharmacokinetics of Lenacapavir, a Long-Acting HIV Capsid Inhibitor: Does Body Site Matter?

Poster 1542

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## Conclusions

- Lenacapavir (LEN) subcutaneous (SC)
  injection in the thigh, upper arm, and gluteal
  region achieved similar or slightly higher
  overall exposures compared to the reference
  abdomen injection
- Geometric mean concentration at 6 months
   (C<sub>6mo</sub>) in all cohorts exceeded the efficacy
   target of inhibitory quotient 4 (IQ4; ie, 4-fold
   greater than the *in vitro* protein-adjusted 95%
   effective concentration [paEC<sub>95</sub>] derived from
   MT-4 cells)
- This study supports the thigh, upper arm, and gluteal region as potential alternate administration sites for SC LEN in future studies

#### Introduction

- LEN is a first-in-class, long-acting, selective inhibitor of HIV-1 capsid function and is currently approved in combination with other antiretrovirals for multidrug-resistant HIV-1 infection in heavily treatment-experienced individuals<sup>1,2</sup>
- LEN dosing regimens consist of 927 mg SC injections (2 x 1.5 mL) in the abdomen every 6 months, along with oral loading doses
- Based on current data, mean trough concentration >15.5 ng/mL, which is the IQ4,<sup>3</sup> is associated with high rates of HIV-1 suppression
- It is common practice to rotate SC administration sites (within the same body site or at a different body site) to mitigate injection site reactions while maintaining similar pharmacokinetic (PK) exposures and providing flexibility in dosing

### Objective

 To investigate the impact of different SC administration sites on LEN PK, in comparison to the abdomen

#### Methods

- This was a Phase 1, open-label, parallel design, single-dose, multicohort study in healthy males and nonpregnant, nonlactating females between the ages of 18–55 years and with body mass index (BMI) 19–30 kg/m<sup>2</sup>
- Participants were enrolled into the thigh, upper arm, gluteal region, or abdomen cohort (n=10 per cohort)
- Participants received a single approved dose of SC LEN 927 mg
   (2 x 1.5 mL injections) either bilaterally in the thigh, upper arm, or gluteal
   region, or in different quadrants of the abdomen
- Plasma PK samples were collected starting on Day 1: 0, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours post dose (Day 10). Additional PK sampling continued weekly or biweekly between Days 15–210, then monthly until Day 270
- PK samples were analyzed for LEN using a validated high performance liquid chromatography-tandem mass spectrometry method
- The PK of LEN was characterized by noncompartmental analysis;
   LEN plasma exposures in the thigh, upper arm, and gluteal region cohorts were descriptively compared to the abdomen cohort as the reference

#### Results

 Sex at birth, age, weight, BMI, and race were comparable between cohorts (Table 1)

Table 1. Baseline characteristics for the thigh, upper arm, gluteal region, and abdomen cohorts

	Thigh (n=10)	Upper arm (n=10)	Gluteal region (n=10)	Abdomen (n=10)		
Sex, %						
Male	50	60	40	50		
Female	50	40	60	50		
Age, years	44 (9.5)	43 (6.7)	40 (9.7)	44 (11.5)		
Weight, kg	77.8 (11.5)	80.3 (13.4)	74.4 (11.6)	74.7 (8.7)		
BMI, kg/m <sup>2</sup>	27.0 (1.6)	27.2 (2.9)	26.9 (2.2)	27.0 (2.4)		
Race, %						
Black or African-American	30	20	0	30		
White	70	80	100	70		

Values for age, weight, and BMI are reported as mean (standard deviation) BMI, body mass index.

### Results (continued)

#### **Pharmacokinetics**

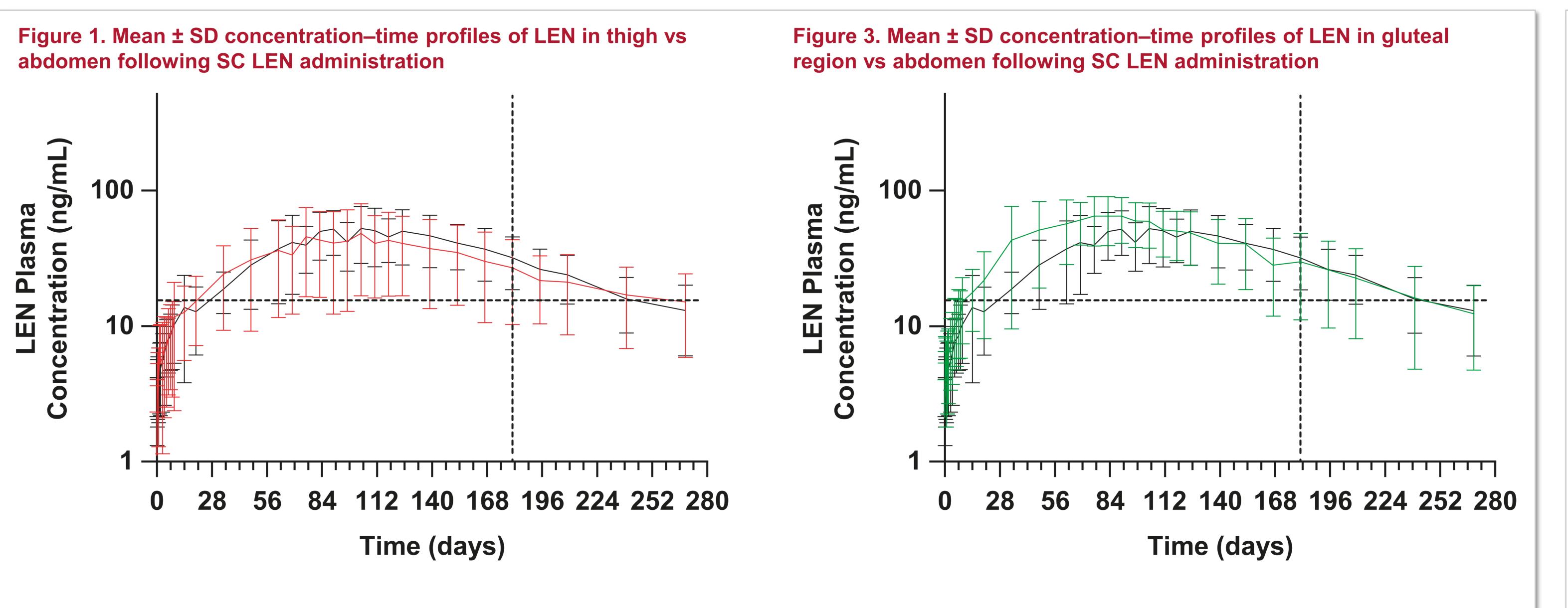
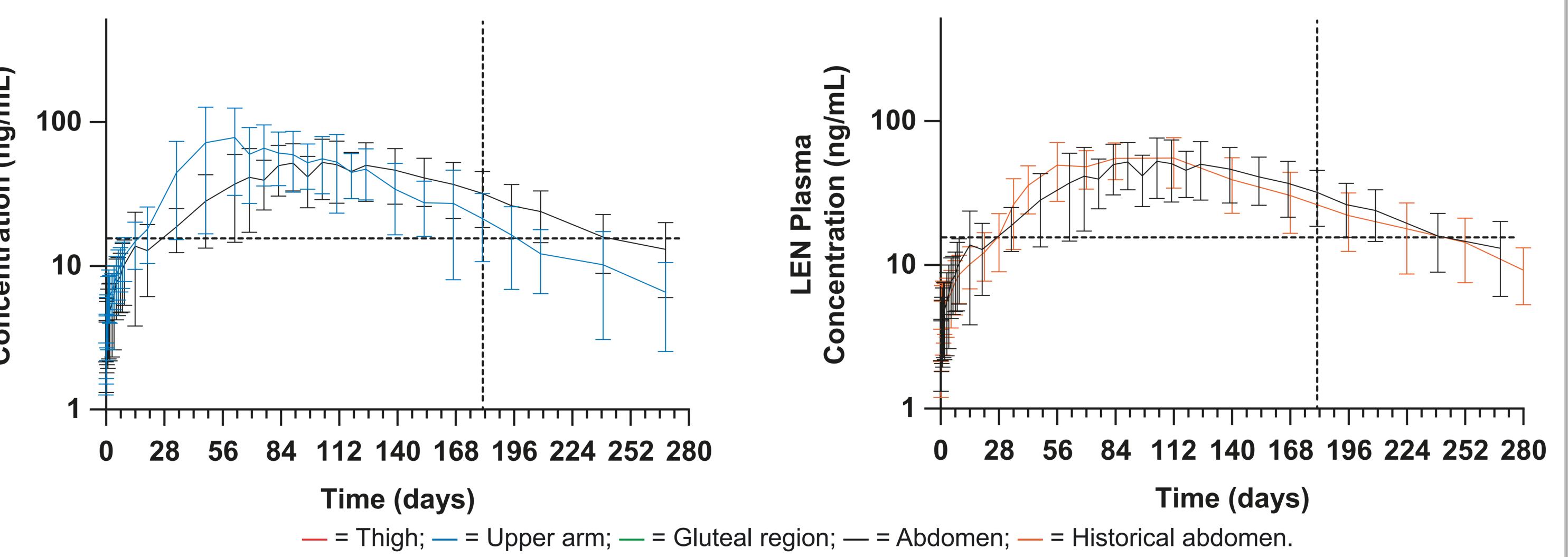


Figure 2. Mean ± SD concentration–time profiles of LEN in upper arm
vs abdomen following SC LEN administration

Figure 4. Mean ± SD concentration—time profiles of LEN in the study abdomen vs historical abdomen following SC LEN administration



Dashed horizontal line represents IQ4 of 15.5 ng/mL; dashed vertical line represents 6-months post dose; 6 months represents 181-days post dose; study duration is up to Day 270; historical abdomen is from a past Phase 1 study<sup>4</sup> using the same formulation, dose, and number of injections for SC LEN. IQ4, 4-fold *in-vitro* protein binding-adjusted 95% effective concentration; LEN, lenacapavir; SD, standard deviation.

Table 2. PK parameters of LEN after SC administration in the thigh, upper arm, gluteal region, and abdomen cohorts

PK Parameter	Thigh (n=10)	Upper arm (n=10)	Gluteal region (n=9ª)	Abdomen (n=8ª)
C <sub>max</sub> (ng/mL)	52.1	75.6	71.2	56.7
	(67.4)	(57.2)	(42.7)	(40.7)
T <sub>max</sub> (h)	2490	1990	2160	2660
	(1950, 3120)	(1150, 2490)	(1660, 2580)	(1870, 3250)
AUC <sub>6mo</sub> b (ng*h/mL)	122,000 <sup>b</sup>	172,000	181,000	144,000
	(73.9)	(45.5)	(36.9)	(38.2)
AUC <sub>last</sub> (ng*h/mL)	164,000 <sup>b</sup>	196,000	220,000	187,000
	(57.6)	(43.9)	(35.9)	(33.3)
AUC <sub>inf</sub> (ng*h/mL)	267,000 <sup>b</sup>	208,000	247,000	223,000
	(26.2)	(43.8)	(35.3)	(34.7)
T <sub>1/2</sub> (h)	1430 <sup>b</sup>	1260	1560	1440
	(1100, 2080)	(1070, 1500)	(1300, 1810)	(1180, 1920)
C <sub>6mo</sub> <sup>c</sup> (ng/mL)	22.6	18.7	25.2	28.6
	(69.9)	(59.9)	(68.0)	(60.6)

Results reported as geometric mean (geometric %CV) except for  $T_{max}$  and  $T_{1/2}$ , which were reported as median (quartile 1, quartile 3)

<sup>a</sup>Participants were either lost to follow up or withdrew early from the study: n=2 from abdomen, and n=1 from gluteal region. <sup>b</sup>6 months represents 181-days post dose. <sup>c</sup>For thigh, AUC<sub>inf</sub> and T<sub>1/2</sub> consist of n=6; AUC<sub>6mo</sub> and AUC<sub>last</sub> consist of n=9.

AUC, area under the curve to 6 months (AUC<sub>6mo</sub>), infinity (AUC<sub>inf</sub>), or the time of last measurable concentration (AUC<sub>last</sub>);  $C_{max}$ , maximum observed concentration; CV, coefficient of variation; CV, half-life; CV, half-life; CV, time to CV

- Overlapping plasma exposures of LEN were observed for the thigh, upper arm, and gluteal region cohorts, compared to the study abdomen cohort (Figure 1–4)
- For the thigh cohort, geometric mean exposures (C<sub>max</sub>, AUC6<sub>mo</sub>, AUC<sub>last</sub>) were similar to the abdomen cohort, with only 8–15% difference (Table 2)
- Geometric mean exposures (C<sub>max</sub>, AUC<sub>6mo</sub>, AUC<sub>last</sub>) were 5–33% and 18–26% higher for the upper arm and gluteal regions cohort, respectively, than the abdomen cohort; these differences were not considered clinically significant (Table 2)
- Geometric mean C<sub>6mo</sub> for all cohorts were higher than the targeted IQ4 (Table 2)
- Exposures in the study abdomen cohort were similar to the historical abdomen cohort from a previous Phase 1 study using the same formulation, dose, and number of injections for SC LEN

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Acknowledgments: Medical writing support was provided by Ashfield MedComms (Macclesfield, UK), an Inizio company, and funded by Gilead Sciences, Inc.

Disclosures: AL, AK, HZ, SL, EM, RP, and RS are all employees and shareholders of Gilead Sciences, Inc.