Long-Acting Subcutaneous Lenacapavir in People With Multi-Drug-Resistant HIV-1: 3-Year Results of the CAPELLA Study

Onyema Ogbuagu[1], Joseph P. McGowan[2], Ann Stapleton[3], Andrew Wiznia[4], Daniel S. Berger[5], Catherine M. Creticos[6], Debbie Hagins[7], Olayemi Osiyemi[8], James Sims[9], David A. Wheeler[10], Hui Wang[11], Nicolas A. Margot[11], Hadas Dvory-Sobol[11], Martin S. Rhee[11], and Sorana Segal-Maurer[12]

[1]Yale School of Medicine, New Haven, Connecticut, USA; [2]Center for AIDS Research and Treatment, Northwell Health, Manhasset, New York, USA; [3]Rimrock Clinic, Eisenhower Health, Rancho Mirage, California, USA; [4]Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA; [5]Northstar Healthcare, Chicago, Illinois, USA; [6]Howard Brown Health, Chicago, Illinois, USA; [7]Coastal District Care Clinic, Savannah, Georgia, USA; [8]Triple O Research Institute PA, West Palm Beach, Florida, USA; [9]St Hope Foundation, Houston, Texas, USA; [10]Infectious Diseases Physicians, Inc., Annandale, Virginia, USA; [11]Gilead Sciences, Inc., Foster City, California, USA; [12]Division of Infectious Diseases, New York–Presbyterian Queens, Flushing, New York, USA.

IDWeek 2024, 16–19 October 2024, Los Angeles, CA, USA

Author Disclosures

Onyema Ogbuagu, MD, Gilead Sciences, Inc. (advisor/consultant, honoraria); ViiV (advisor/consultant); Janssen (advisor/consultant). **Joseph P. McGowan, MD** has nothing to disclose. **Ann Stapleton, MD,** GSK (consultant). **Andrew Wiznia, MD,** Gilead Sciences, Inc. (advisor/consultant), Janssen (advisor/consultant). **Daniel S. Berger, MD,** Gilead Sciences, Inc. (stocks/bonds). **Catherine M. Creticos, MD,** Gilead Sciences, Inc. (speaker); Theratechnologies (speaker); ViiV (speaker). **Debbie Hagins, MD,** Gilead Sciences, Inc. (advisor/consultant). **Olayemi Osiyemi MD,** Gilead Sciences, Inc. (advisor/consultant, speaker); Merck (advisor/consultant); ViiV (advisor/consultant, speaker). **James Sims, MD** has nothing to disclose. **David A. Wheeler, MD,** Gilead Sciences, Inc. (research funding); Janssen (research funding); AstraZeneca (research funding). **Hui Wang, PhD, Nicolas A. Margot, MA, Hadas Dvory-Sobol, PhD,** and **Martin S Rhee, MD,** are all employees and shareholders of Gilead Sciences, Inc. **Sorana Segal-Maurer, MD,** at the time of study conduct and data analysis: Gilead Sciences, Inc. (advisor/consultant, grant/research support, honoraria); Janssen (honoraria); ViiV (honoraria); Theratechnologies (advisor/consultant). **Sorana Segal-Maurer, MD,** is now an employee and shareholder of Gilead Sciences, Inc.

All relevant financial disclosures have been mitigated.

Background

- Lenacapavir (LEN) is a first-in-class, long-acting HIV-1 capsid inhibitor which targets viral nuclear import, virion assembly, and capsid core assembly, thereby inhibiting virion production[1]
- LEN is indicated for the treatment of multi-drug-resistant (MDR) HIV-1, in combination with other antiretrovirals[2]
- LEN is administered twice-yearly by subcutaneous (SC) injection following oral lead-in dosing[2]
- The approval of LEN was based on the results of the ongoing Phase 2/3 CAPELLA trial (NCT04150068), in which LEN, combined with an optimized background regimen (OBR), resulted in a high rate of virologic suppression (VS) in participants with MDR HIV-1[3]
  - LEN achieved its primary endpoint as a functional monotherapy when added to a failing regimen: 88% of participants on LEN had a ≥0.5-$\log_{10}$ decline in HIV-1 RNA versus 17% on placebo ($P<0.001$)[3]
  - 82% of participants achieved VS (missing=excluded analysis) at Week 104[4]

Objective: To assess the longer-term efficacy and safety of LEN in people with MDR HIV-1 through Week 156

LEN, lenacapavir; **MDR,** multi-drug-resistant; **OBR,** optimized background regimen; **PWH,** people with HIV; **SC,** subcutaneous; **VS**, virologic suppression.

1. Link JO, et al. *Nature*. 2020;584:614–618. 2. FDA. Sunlenca® Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf (Accessed October 2024) 3. Segal-Maurer S, et al. *N Engl J Med*. 2022;386:1793–1803. 4. Ogbuagu O, et al. *Clin Infect Dis*. 2024 Aug 29:ciae423. Online ahead of print.

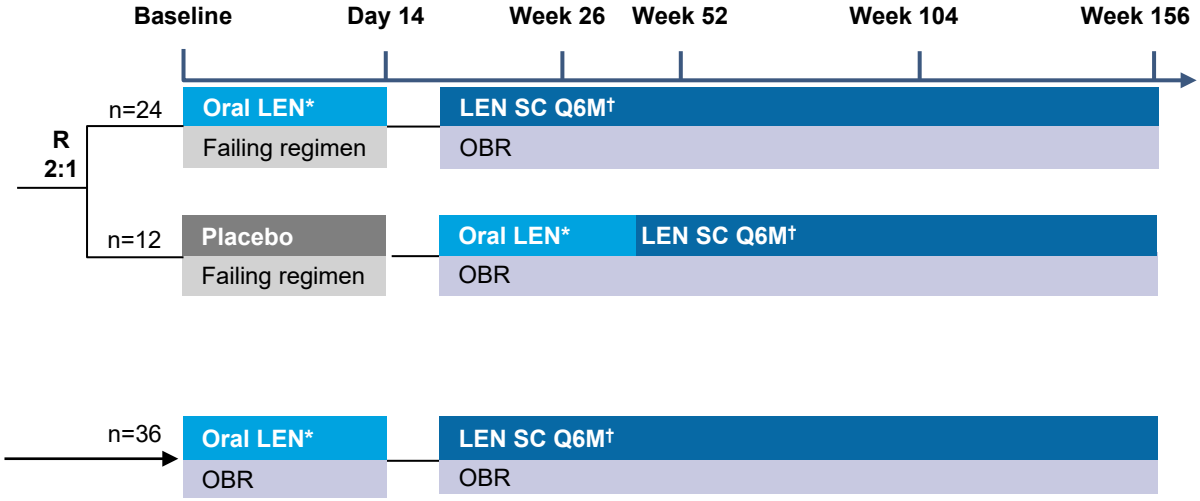
Study Design

Key eligibility criteria:
- HIV-1 RNA ≥400 c/mL
- Receiving a failing ARV regimen
- Resistance to ≥2 ARVs from ≥3 of the four main classes (NRTI, NNRTI, PI, INSTI)

Pre-randomization repeat HIV-1 RNA
- Decline ≥0.5 log c/mL (vs screening); or
- <400 c/mL

No → **Cohort 1** Randomized, double blind

Yes → **Cohort 2** Open label



- CAPELLA is an ongoing, Phase 2/3 study in people with MDR HIV-1[1,2]
  - Participants received a 2-week oral LEN lead-in followed by SC LEN every 6 months (Q6M) combined with an investigator-selected optimized background regimen (OBR)

*Days 1 and 2: 600 mg; Day 8, 300 mg. †927 mg as two 1.5-mL injections in the abdomen on Day 15, then Q6M.

ARV, antiretroviral; **c/mL**, copies/mL; **INSTI,** integrase strand transfer inhibitor; **LEN**, lenacapavir; **MDR,** multi-drug-resistant; **NRTI,** nucleos(t)ide reverse transcriptase inhibitor; **NNRTI,** non-nucleoside reverse transcriptase inhibitor; **OBR**, optimized background regimen; **PI,** protease inhibitor; **Q6M**, every 6 months; **R,** randomisation; **SC**, subcutaneous.

1. Segal-Maurer S, et al. *N Engl J Med*. 2022;386:1793–1803. 2. Ogbuagu O, et al. *Lancet HIV*. 2023;10:e497–e505.

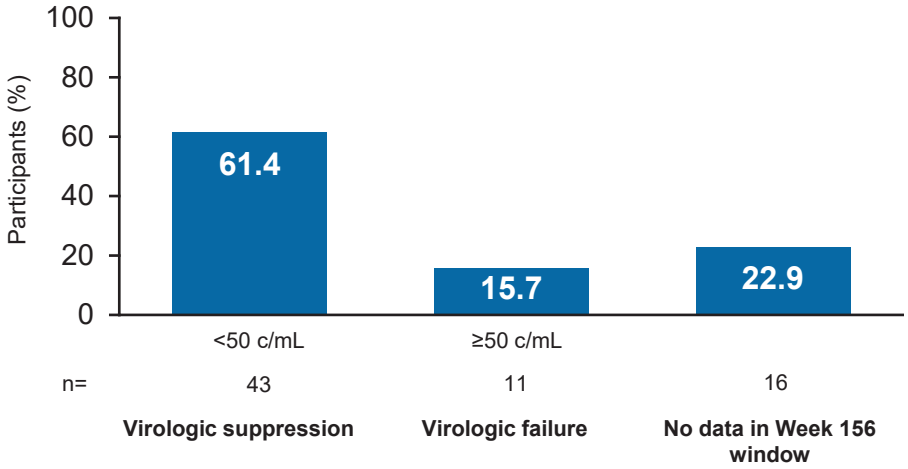
Baseline Demographics

	Total N=72
Median (range) age, years	52 (23–78)
Sex at birth, n (%)	
Male	54 (75.0)
Female	18 (25.0)
Race, n (%)*	
Asian	15 (21.1)
Black	27 (38.0)
White	29 (40.8)
HIV-1 RNA	
Median (range), $\log_{10}$ c/mL	4.5 (1.3–5.7)
>100,000 c/mL, n (%)	14 (19.4)
CD4 cell count	
Median (range), cells/μL	150 (3–1296)
<200 cells/μL, n (%)	46 (63.9)
<50 cells/μL, n (%)	16 (22.2)
Median (range) number of prior ARVs	11 (2–25)
Known resistance to ≥2 drugs in class, n (%)	
NRTI	71 (98.6)
NNRTI	70 (97.2)
PI	58 (80.6)
INSTI	50 (69.4)
All four major classes	33 (45.8)

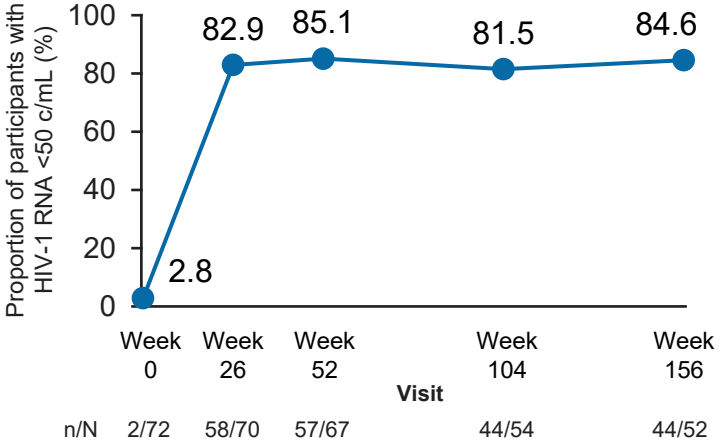
*Collection of race information not permitted by local regulations, n=1 (Cohort 1); participant excluded from percentage calculation.
ARV, antiretroviral; **c/mL**, copies/mL; **INSTI**, integrase strand-transfer inhibitor; **NRTI,** nucleos(t)ide reverse transcriptase inhibitor; **NNRTI,** non-nucleoside reverse transcriptase inhibitor; **PI**, protease inhibitor.

Virologic Outcomes

A: FDA snapshot analysis at Week 156 (N=70)*



B: HIV-1 RNA <50 c/mL by missing=excluded analysis from baseline to Week 156†

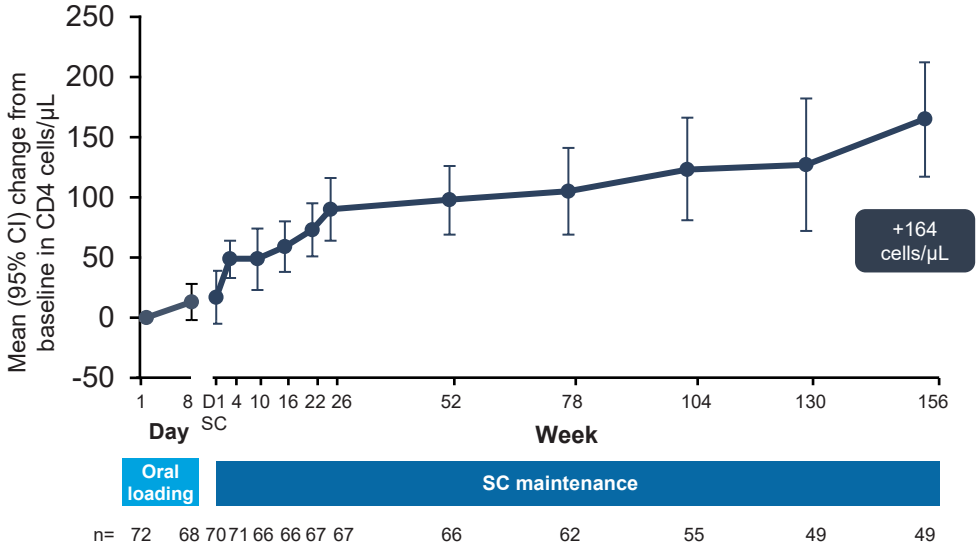


- At Week 156, 72% (52/72) of participants remained on study‡
- Overall, 98% of SC injections were within ± 14 days of the scheduled doses

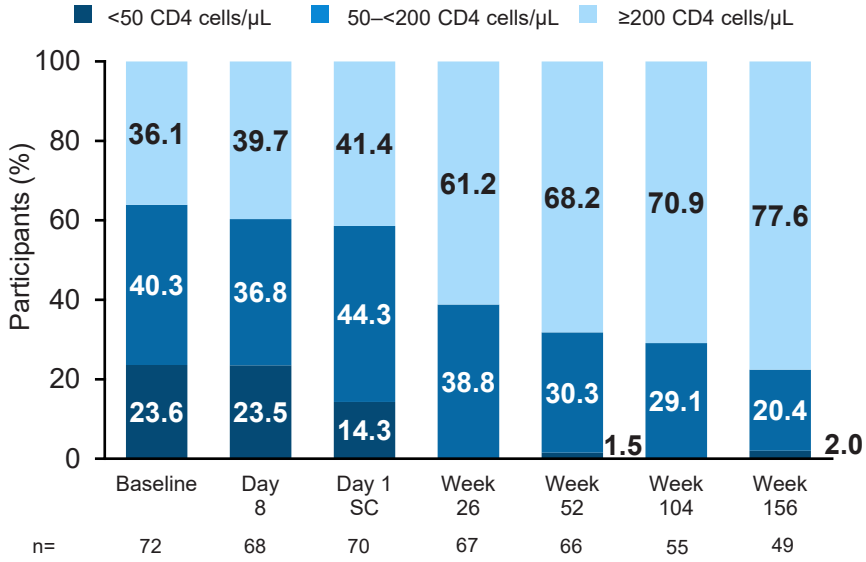
*Participants who had missing HIV-1 RNA at Week 156 and had completed the study before reaching the upper limit of the analysis window for Week 156 were excluded (n=2).
†The denominator for percentages is the number of participants with non-missing HIV-1 RNA values at each time point. ‡20 participants prematurely discontinued study prior to Week 156: Lost to follow-up (n=8), withdrew consent (n=5), investigator's discretion (n=2), adverse event (n=2), death (n=3).
c/mL, copies/mL; **FDA,** Food and Drug Administration; **SC**, subcutaneous.

CD4 Cell Count by Category and Mean Change from Baseline

A. Mean Change from Baseline in CD4 Cell Count



B. CD4 Cell Count Change by Category



- From baseline to Week 156, the proportion of participants with CD4 count <200 and <50 cells/µL decreased from 64% to 22%, and 24% to 2%, respectively

CI, confidence interval; **D**, day; **SC**, subcutaneous.

Emergent LEN Resistance

	Total N=72
Emergent LEN resistance (M66I; Q67H/K/N; K70H/N/R/S; N74D/H/K; A105S/T; T107A/C/N/S)	14
No fully active agents in OBR	4
Inadequate adherence to OBR*	10
Resuppressed after LEN resistance emergence whilst remaining on LEN	5
With OBR change	2
Without OBR change	3
Did not resuppress after LEN resistance emergence	9
Continued study drug†	6
Discontinued study drug for reasons not related to efficacy‡	3

- Overall, 14 people developed resistance to LEN, nine by Week 52 and five between Week 52 and Week 104
  - No new cases of LEN resistance emerged between Week 104 and Week 156
  - Two participants with resistance detected earlier developed additional mutations§
- All 14 participants with LEN resistance had no fully active drugs in OBR or inadequate OBR adherence
  - Median (interquartile range [IQR]) CD4 cell count change from baseline to Week 156: 82 (48–399) cells/μL

*Based on OBR plasma concentrations. †Returned to baseline viral load n=2, >1 log reduction n=3, mean log reduction from Day 1 for the 4 who did not return to baseline: -1.64 . ‡Due to: death (n=1); investigator's discretion due to non-compliance (n=1); lost to follow-up (n=1). §1 participant had emergence of K70R+T107N with existing Q67H (reduction in LEN susceptibility from 4.5- to 85-fold of WT), and 1 participant had emergence of T107T/N with existing K70N+N74K (no LEN susceptibility data for triple mutant).
c/mL, copies/mL; **IQR,** interquartile range; **LEN,** lenacapavir; **OBR,** optimized background regimen; **RAM,** resistance-associated mutation; **VL,** viral load, **W,** week.

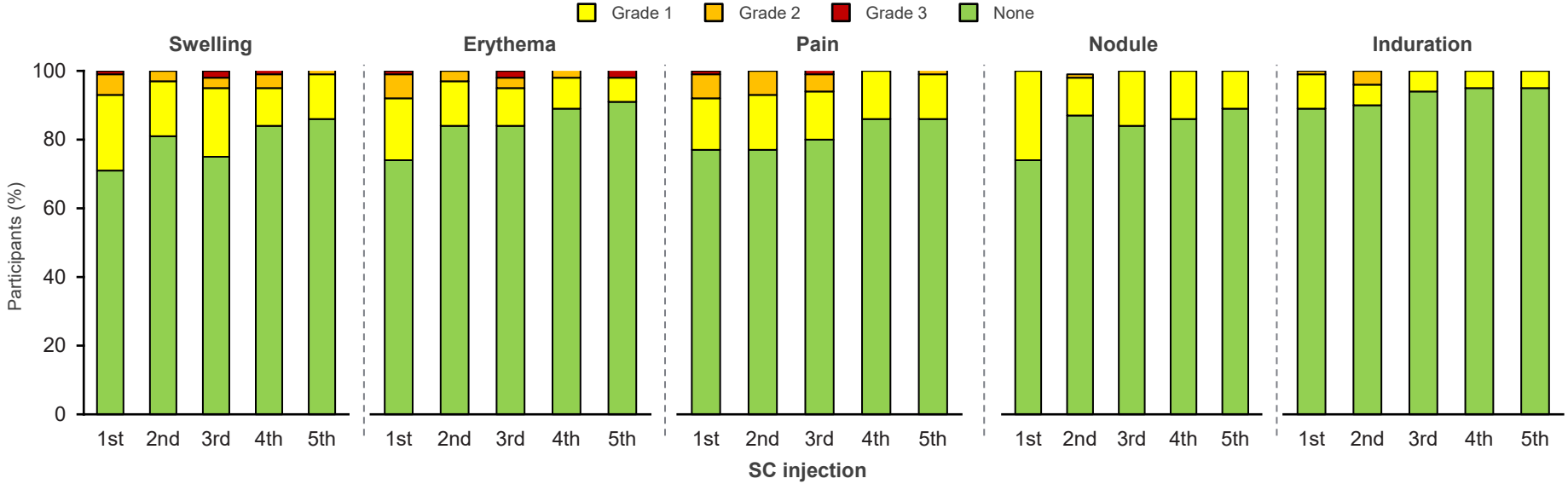
Safety (LEN + OBR)

- The median duration of follow-up on LEN was 165 (IQR 146–178) weeks

n (%)	Total N=72
Most common TEAEs (occurring ≥15% of participants, excluding ISRs and COVID-19)	
Diarrhea	15 (20.8)
Nausea	14 (19.4)
Urinary tract infection	12 (16.7)
Cough	12 (16.7)
TEAEs	71 (98.6)
Grade ≥3	31 (43.1)
Treatment-related TEAEs	57 (79.2)
Grade 3	6 (8.3)*
Serious TEAEs	22 (30.6)
TEAEs leading to premature study drug discontinuation	2 (2.8)†
All deaths (unrelated to LEN)	3 (4.2)‡

TEAEs occurring in ≥10% of participants: constipation (13.9%), headache (13.9%), pyrexia (13.9%), abdominal distention (11.1%), arthralgia (11.1%), back pain (11.1%)
*Grade 3 treatment-related TEAEs: ISR, n=4; immune reconstitution inflammatory syndrome, n=1; abdominal abscess, n=1; rash, n=1. †Due to injection site nodule, n=2.
‡Deaths due to: malignant neoplasm, n=1; acute respiratory failure, n=1; unknown cause, n=1.
IQR, interquartile range; **ISR**, injection-site reaction; **TEAE**, treatment-emergent adverse event.

Incidence and Severity of Most Common SC LEN-related ISRs



- ISRs experienced by participants were mostly Grade 1/2 (97.2%) and decreased in frequency over time
- Two participants discontinued study drug due to Grade 1 injection site nodules (n=1 previously reported)
- The median (Q1, Q3) duration of swelling, erythema, pain, nodules, and induration was 8 (4, 15) days, 5 (3, 8) days, 3 (2, 5) days, 288 (155, 548) days, and 190 (67, 410) days, respectively

*Percentage denominators are the number of participants who received an injection at that visit. Percentages may not total 100% due to rounding.
ISR, injection site reaction; **LEN**, lenacapavir, **SC**, subcutaneous.

Conclusions

- LEN combined with an OBR continued to result in high and sustained rates of VS through Week 156 in heavily treatment-experienced people with HIV (HTE PWH)
- Clinically relevant increases in CD4 cell counts were observed from baseline to Week 156
  - CD4 cell counts continued to increase between Week 104 and Week 156
- Emergence of LEN resistance was associated with inadequate OBR adherence and OBRs without fully active agents
- LEN was well tolerated, consistent with previous data
- These longer-term data support the use of LEN for the treatment of HTE PWH with MDR HIV-1

HTE PWH, heavily treatment-experienced people with HIV; **MDR**, multi-drug-resistant; **OBR**, optimized background regimen; **VS**, virologic suppression.

Acknowledgements

- We extend our thanks to the CAPELLA patients, their families, and all participating investigators
- This analysis was funded by Gilead Sciences, Inc.
- All authors contributed to and approved the presentation; medical writing support was provided by Jessica Adams, PharmD, of Gilead Sciences, Inc. Editorial support was provided by Ashfield MedComms, an Inzio company, and was funded by Gilead Sciences, Inc.

- Correspondence: Onyema Ogbuagu, onyema.ogbuagu@yale.edu