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Presentation #151

# Efficacy and Safety of Lenacapavir, Teropavimab, and Zinlirvimab: Phase 2 Week 26 Primary Outcome

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# Disclosures

**Onyema Ogbuagu** reports advisory board participation for Gilead Sciences, Inc. and ViiV.

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# Background

- Lenacapavir (LEN), an HIV-1 capsid inhibitor, can be administered subcutaneously (SC) twice-yearly (Q6M) and is approved for the treatment of multidrug-resistant HIV-1 infection[1]

- Teropavimab (TAB) and zinlirvimab (ZAB) are broadly neutralizing antibodies (bNAbs) with extended half-lives dosed Q6M[2]
  - TAB targets the CD4-binding site and ZAB targets the V3 loop glycan on the HIV-1 envelope

- In a proof-of-concept Phase 1b study (NCT04811040), the combination of LEN, TAB, and ZAB maintained virologic suppression (HIV-1 RNA <50 copies/mL) for 6 months in 18/20 people with HIV-1 highly susceptible to both bNAbs[3]

**Objective: To evaluate the Phase 2 efficacy, safety and pharmacokinetics (PK) of switching to LEN, TAB, and ZAB Q6M versus staying on an oral stable baseline regimen**

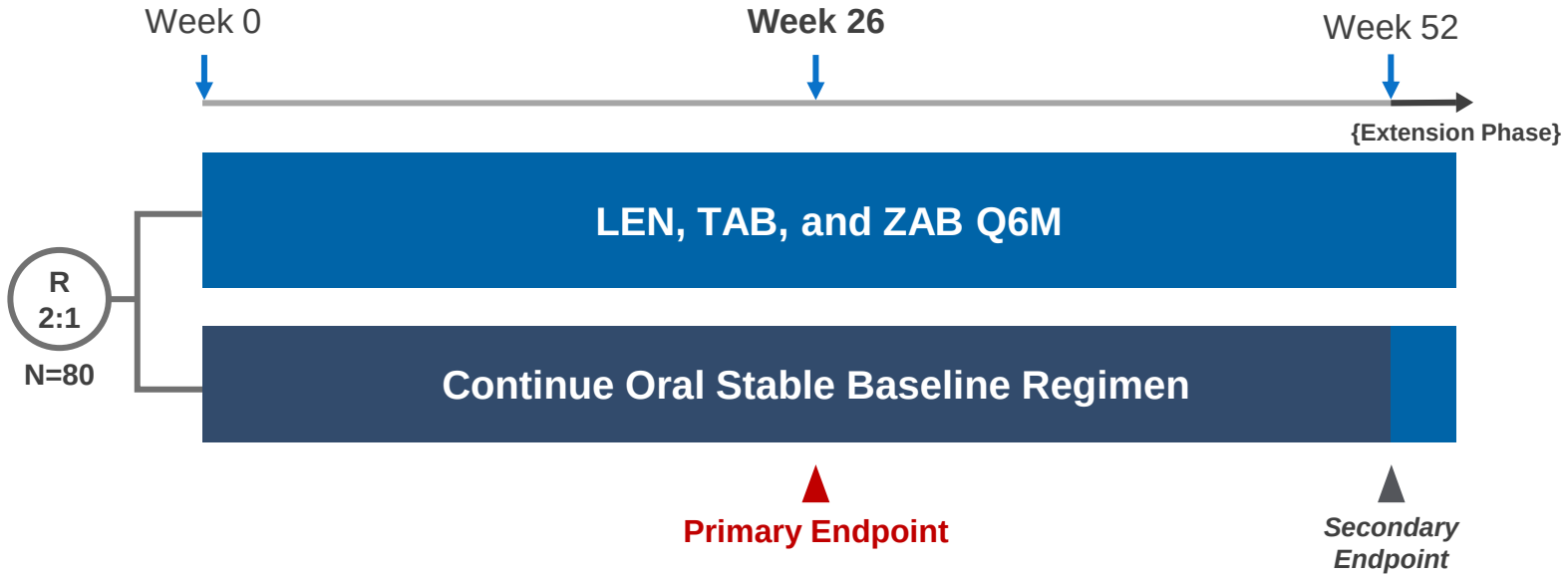

1. Sunlenca® US Prescribing Information, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf [Accessed March 2025].
2. Gautam R, et al. *Nat Med*. 2018;24:610–6.
3. Eron J, et al. Lancet HIV. 2024;11:e146–55.


**bNAb,** broadly neutralizing antibody; **LEN,** lenacapavir; **PK,** pharmacokinetics; **Q6M**, every 6 months; **SC,** subcutaneously; **TAB**, teropavimab; **ZAB,** zinlirvimab.

# Phase 2 Study Design[a]

**Key inclusion criteria**

- Age 18–65 years
- HIV-1 RNA <50 copies/mL for ≥12 months
- On stable oral ART (≤2 classes) for ≥12 months
- CD4+ T-cell count ≥200 cells/µL
- HBV negative
- Highly susceptible to **both** bNAbs ($IC_{90}$ ≤2 µg/mL)[b]




**Primary Outcome (Efficacy):** HIV-1 RNA ≥50 copies/mL at Week 26 per FDA snapshot algorithm

**Secondary Outcomes:** Safety (adverse events); change from baseline in CD4+ T-cell count, PK of LEN, TAB, and ZAB; anti-drug antibodies (ADAs) at Week 26

[a]NCT05729568. [b]By PhenoSense® mAb Assay (Monogram Biosciences).
**ADAs,** anti-drug antibodies; **ART,** antiretroviral therapy; **bNAb,** broadly neutralizing antibody; **HBV,** hepatitis B virus; **$IC_{90}$,** 90% inhibitory concentration; **LEN,** lenacapavir; **PK,** pharmacokinetics; **Q6M,** every 6 months; **R,** randomized; **TAB,** teropavimab; **ZAB,** zinlirvimab.

# Phase 2 Dose Rationale

- In the Phase 1b study, all participants who received TAB and ZAB 30 mg/kg remained virologically suppressed on the study regimen
- A fixed dose of 2550 mg for both TAB and ZAB was predicted to produce similar exposures to the 30 mg/kg weight-based dose[a]

| LEN, TAB, and ZAB Phase 2 Dosing Schedule | |
|---|---|
| **Q6M (+/– 2 weeks)** | • SC LEN 927 mg[b]<br>• IV TAB 2550 mg<br>• IV ZAB 2550 mg |

**Fixed doses of TAB 2550 mg and ZAB 2550 mg were selected for the Phase 2 study**

[a]Modeled on weight distribution of a prior Phase 3 HIV-1 treatment study. [b]Loading doses of oral LEN 600 mg were administered on Days 1 and 2.
**IV,** intravenous; **LEN,** lenacapavir; **Q6M**, every 6 months; **SC,** subcutaneous; **TAB**, teropavimab; **ZAB,** zinlirvimab.

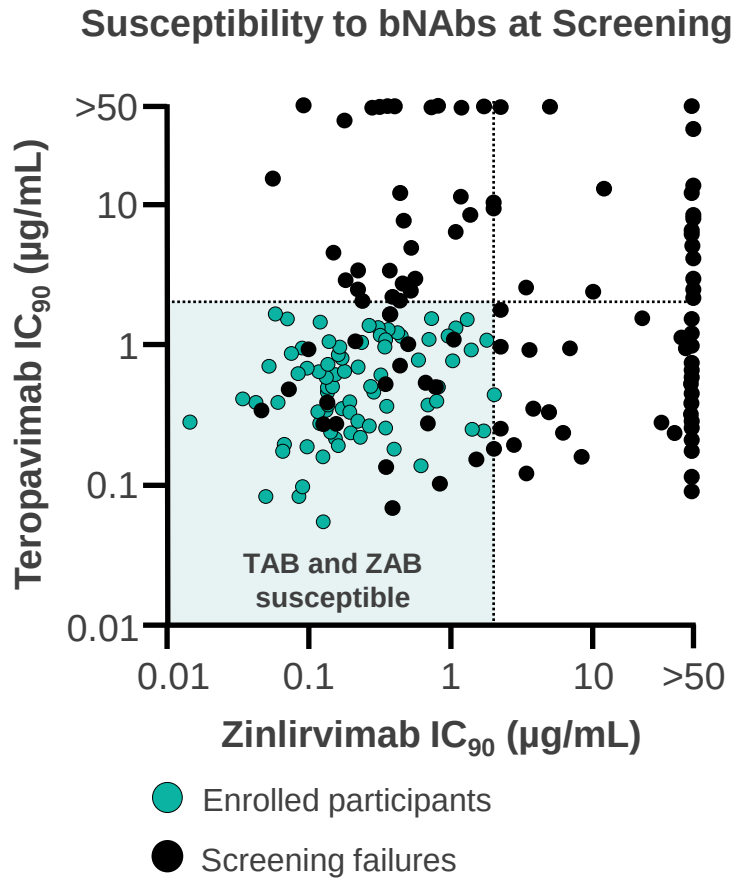
# Participant Disposition and bNAb Susceptibility

**Screened (N=241)**
**Susceptibility results (n=200)[a]**

**Susceptible to TAB and ZAB (n=99)[b]**

**Randomized and dosed (N=80)[c]**

| **LEN, TAB, and ZAB n=53** | **Oral Stable Baseline Regimen n=27** |
|---|---|
| *Discontinued study (n=1)[d]* | *Discontinued study (n=1)[e]* |
| **Treated with follow-up to W26 n=52** | **Treated with follow-up to W26 n=26** |




[a]41 with assay failure, 195 with screening data and 5 with results from the Phase 1b study; [b]TAB only: 47 (24%); ZAB only: 31 (16%); neither: 23 (12%). [c]84 participants met all eligibility criteria; 1 eligible but not randomized (participant decision); 3 randomized but not dosed (participant decision). [d]Discontinued study drug and study due to investigator's discretion (relocation). [e]Discontinued oral stable baseline regimen and study due to adverse event (metastatic pancreatic carcinoma).
**bNAb,** broadly neutralizing antibody; **$IC_{90}$,** 90% inhibitory concentration; **LEN,** lenacapavir; **TAB,** teropavimab; **W,** week; **ZAB,** zinlirvimab.

# Baseline Characteristics

| | LEN, TAB, and ZAB n=53 | Oral Stable Baseline Regimen n=27 |
|---|---|---|
| **Median (range) age, years** | 46 (20–65) | 57 (28–65) |
| **Female sex at birth, n (%)** | 8 (15) | 4 (15) |
| **Race, n (%)** | | |
| Asian | 1 (2) | 1 (4) |
| Black | 21 (40) | 8 (30) |
| White | 28 (53) | 16 (59) |
| Other | 3 (6) | 2 (7) |
| **Hispanic or Latine ethnicity, n (%)** | 13 (25) | 7 (26) |
| **Median (range) weight, kg** | 93 (56–156) | 87 (58–157) |
| **Median (IQR) BMI, kg/m$^2$** | 29.2 (25.5–33.8) | 29.2 (25.5–32.0) |
| **Median (IQR) CD4+ T-cell count, cells/μL** | 710 (552–895) | 738 (583–869) |
| **USA region[a], n (%)** | 48 (91) | 19 (70) |

[a]Ex-US regions include Australia, Canada, and Puerto Rico. Participants were enrolled across 34 sites.
**BMI,** body mass index; **IQR,** interquartile range; **LEN**, lenacapavir; **TAB,** teropavimab; **ZAB**, zinlirvimab.

# Week 26 Virologic Outcomes (FDA Snapshot Algorithm)

| Participants, n (%) | LEN, TAB, and ZAB n=53 | Oral Stable Baseline Regimen n=27 |
|---|---|---|
| **HIV-1 RNA ≥50 copies/mL** | 1 (1.9) | 0 |
| **HIV-1 RNA <50 copies/mL** | 51 (96.2) | 26 (96.3) |
| **No virologic data in Week 26 window[a]** | 1[b] (1.9) | 1[c] (3.7) |

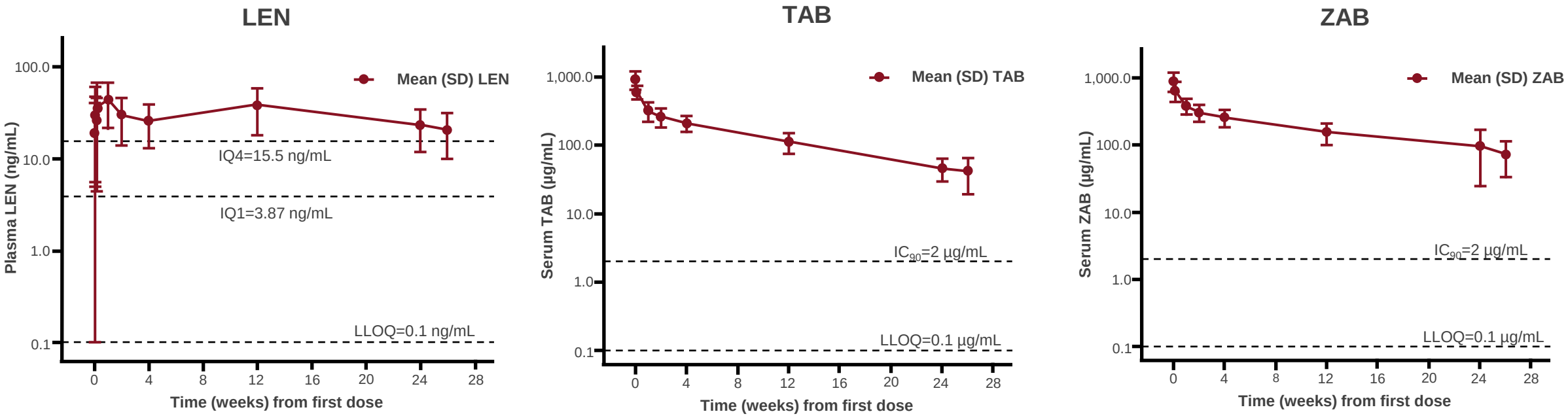
— Mean CD4+ T-cell counts increased at Week 26 in both treatment arms with no difference between groups (p=0.2)[d]

**Efficacy of LEN, TAB, and ZAB at Week 26 was comparable to continuing daily oral ART**

[a]Last available HIV-1 RNA was <50 copies/mL for both participants with no virologic data in the Week 26 window. [b]Discontinued study drug due to investigator's discretion (relocation). [c]Discontinued stable baseline regimen due to adverse event (metastatic pancreatic carcinoma). [d]The difference was calculated as the difference in least-squares means. Mean (SD) change: +23 (143) cells/μL in the LEN, TAB, and ZAB group and +69 (203) cells/μL in the stable baseline regimen group.
**LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

# Pharmacokinetics and Anti-Drug Antibodies

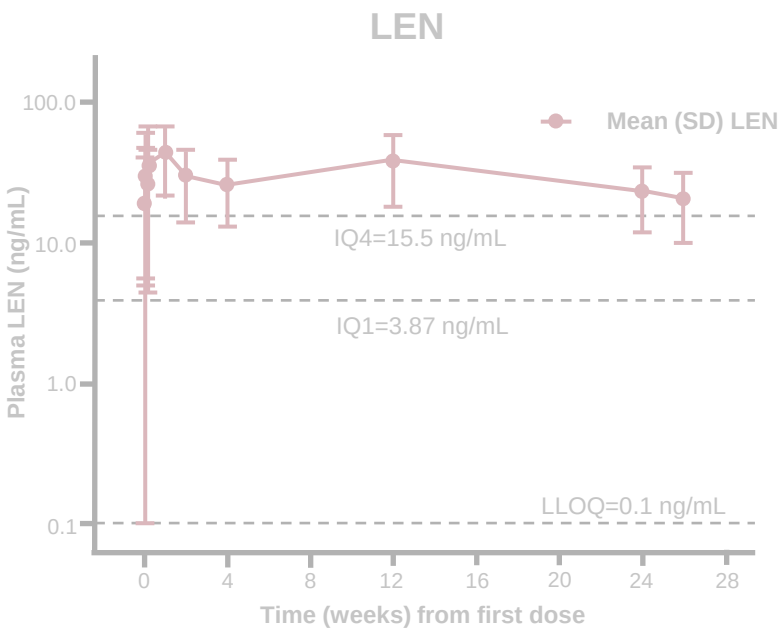
— Mean therapeutic concentrations of LEN, TAB, and ZAB were maintained through Week 26

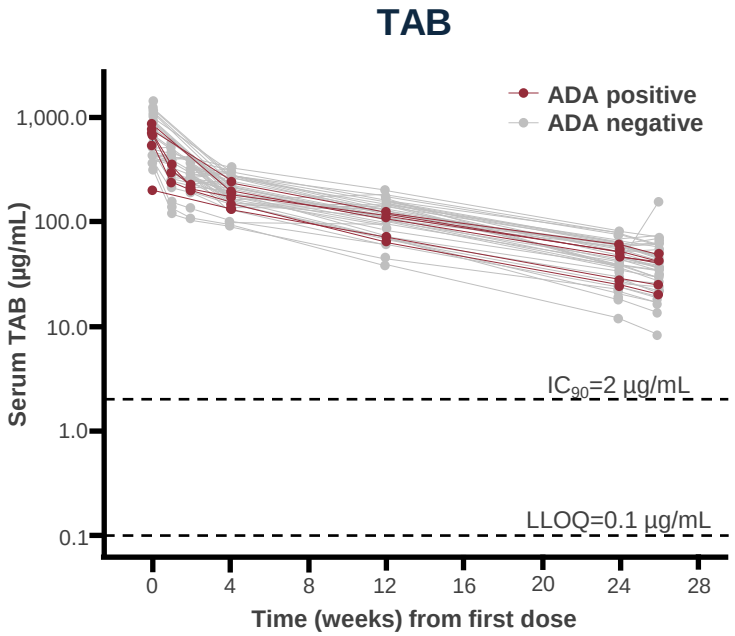


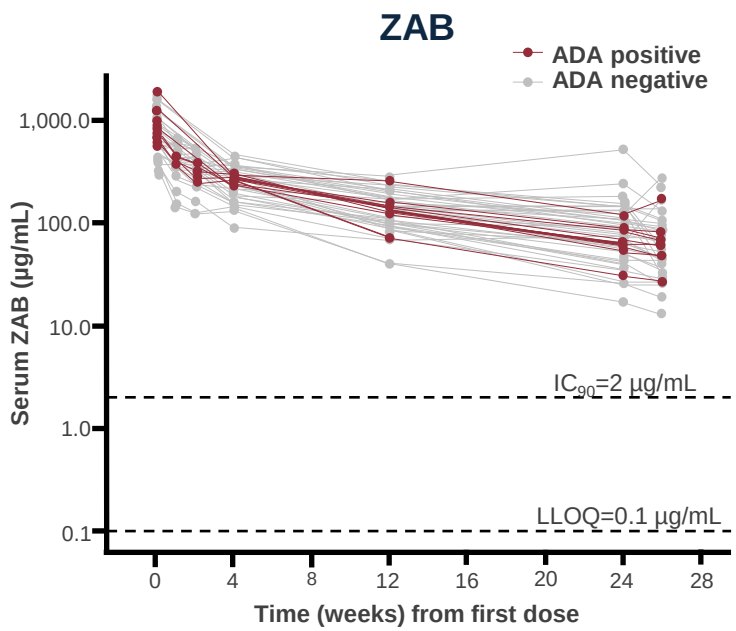

$IC_{90}$, 90% inhibitory concentration; **IQ,** inhibitory quotient; **LEN,** lenacapavir; **LLOQ**, lower limit of quantification; **PK,** pharmacokinetic; **TAB,** teropavimab; **ZAB,** zinlirvimab.

# Pharmacokinetics and Anti-Drug Antibodies

— Mean therapeutic concentrations of LEN, TAB, and ZAB were maintained through Week 26



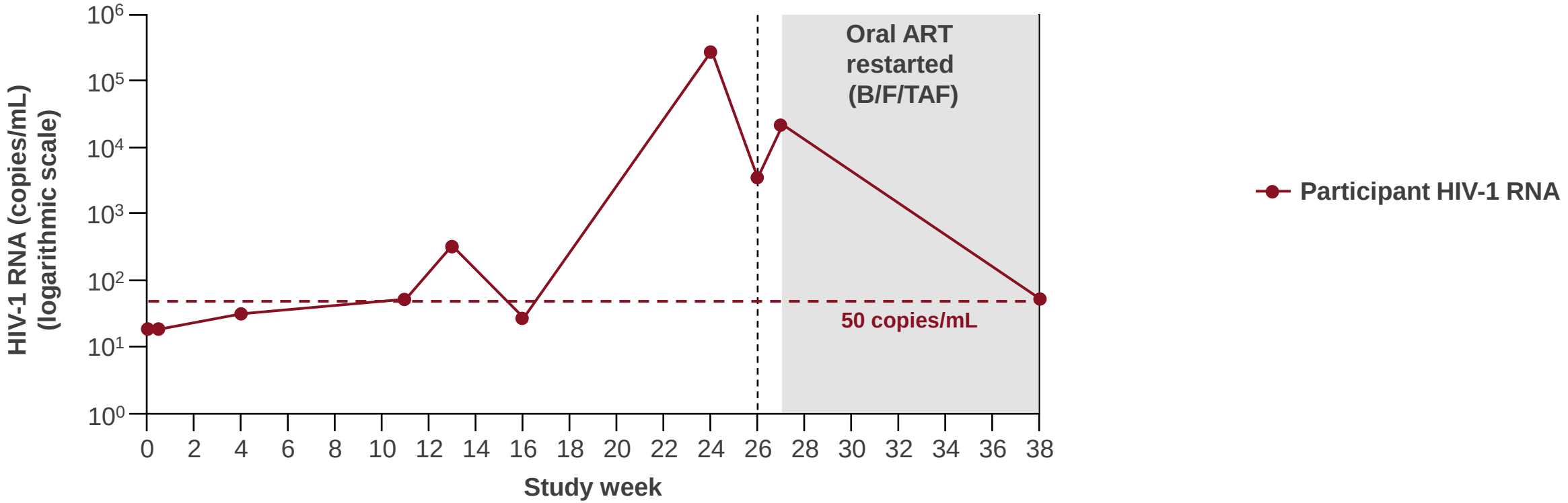

Treatment-emergent ADAs against: TAB in 6 (11.3%) participants, ZAB in 9 (17.0%) participants[a]

**PK and safety profiles were similar in participants with and without ADAs**

[a]Median (minimum, maximum) time to onset of ADAs against TAB and ZAB was 182 (83, 183) and 84 (81, 183) days, respectively.

**ADA,** anti-drug antibody; **$IC_{90}$,** 90% inhibitory concentration; **IQ,** inhibitory quotient; **LEN,** lenacapavir; **LLOQ**, lower limit of quantification; **PK,** pharmacokinetic; **TAB,** teropavimab; **ZAB,** zinlirvimab.

# Participant with Virologic Failure

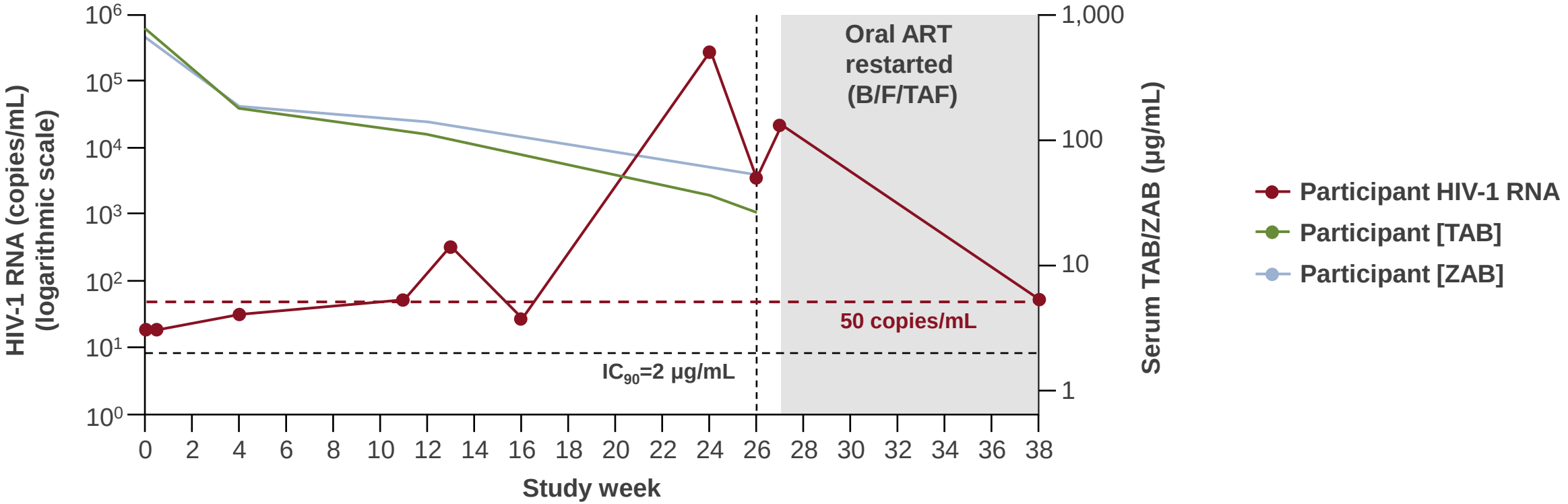



**Week 12:** Resuppressed with no change in regimen.

**Week 24:** Resistance to LEN detected (Q67H in capsid); loss of ZAB susceptibility; TAB susceptibility unchanged from baseline.

**ART,** antiretroviral therapy; **B/F/TAF,** bictegravir/emtricitabine/tenofovir alafenamide; **LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

# Participant with Virologic Failure (TAB and ZAB PK)




**Week 12:** Resuppressed with no change in regimen.

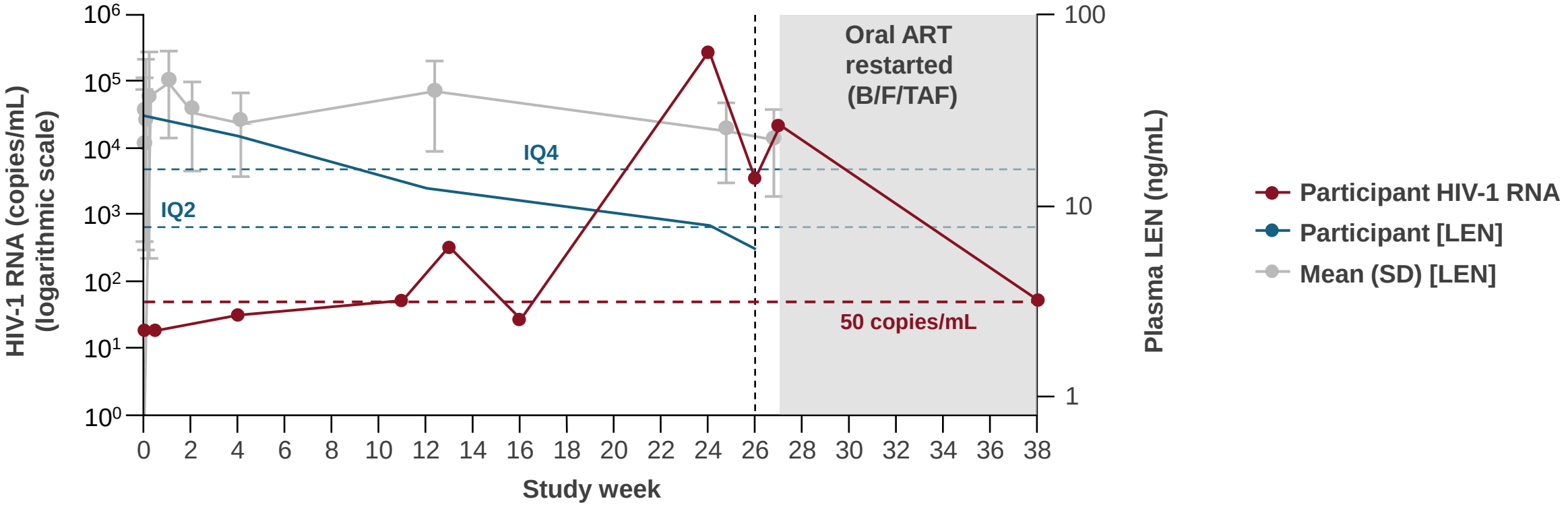
**Week 24:** Resistance to LEN detected (Q67H in capsid); loss of ZAB susceptibility; TAB susceptibility unchanged from baseline.

— No ADAs detected

— TAB and ZAB concentrations similar to mean concentrations through Week 26

**ADAs,** anti-drug antibodies; **ART,** antiretroviral therapy; **B/F/TAF,** bictegravir/emtricitabine/tenofovir alafenamide; **$IC_{90}$,** 90% inhibitory concentration; **LEN,** lenacapavir; **PK,** pharmacokinetics; **TAB,** teropavimab; **ZAB,** zinlirvimab.

# Participant with Virologic Failure (LEN PK)




**Week 12:** Resuppressed with no change in regimen.

**Week 24:** Resistance to LEN detected (Q67H in capsid); loss of ZAB susceptibility; TAB susceptibility unchanged from baseline.

- No ADAs detected
- TAB and ZAB concentrations similar to mean concentrations through Week 26
- LEN concentrations were lower than one standard deviation below the mean by Week 12

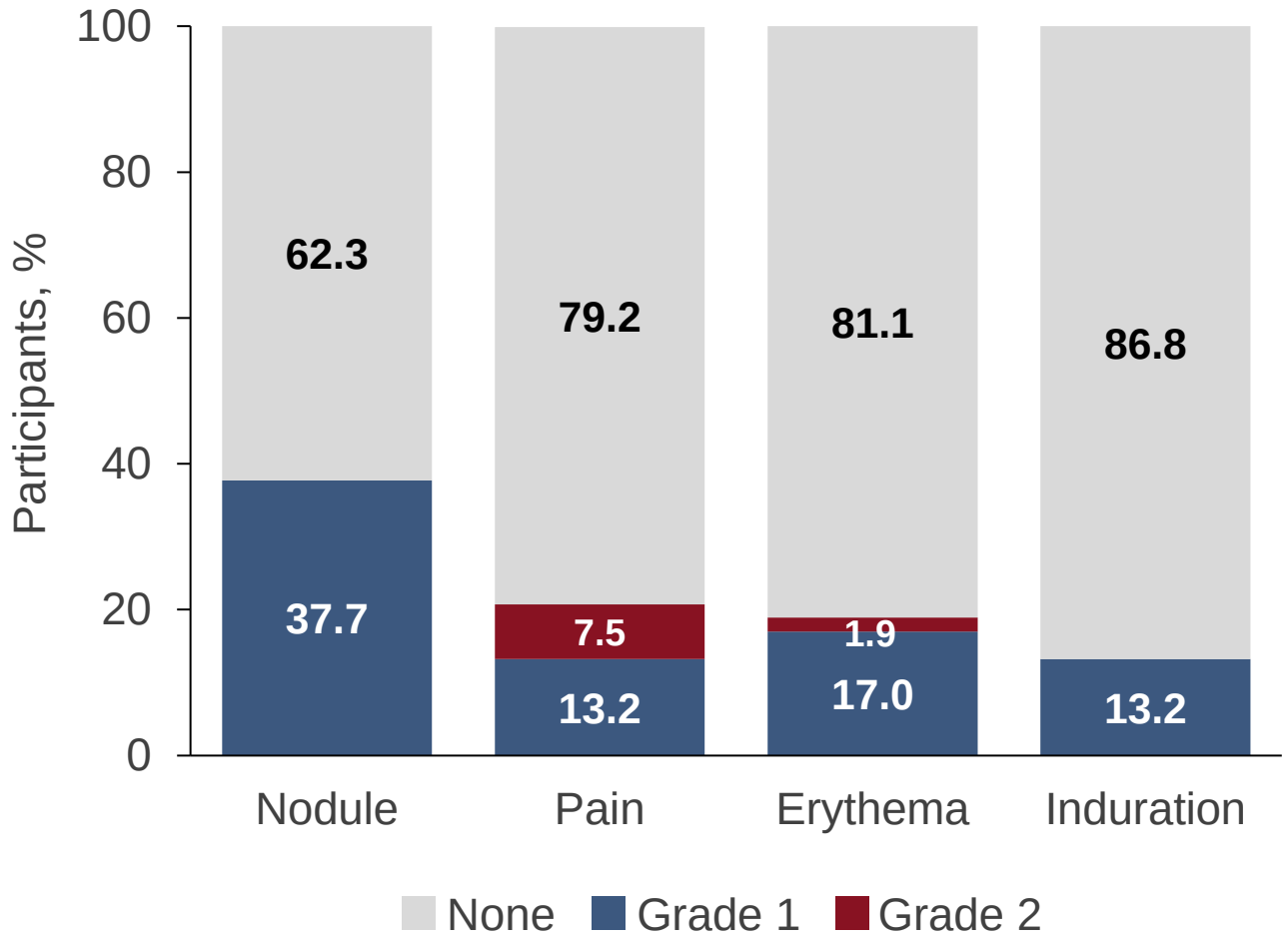
**ADAs,** anti-drug antibodies; **ART,** antiretroviral therapy; **B/F/TAF,** bictegravir/emtricitabine/tenofovir alafenamide; **IQ,** inhibitory quotient; **LEN,** lenacapavir; **PK,** pharmacokinetics; **TAB,** teropavimab; **ZAB,** zinlirvimab.

# Safety Overview

| Participants, n (%) | LEN, TAB, and ZAB n=53 | Oral Stable Baseline Regimen n=27 |
|---|---|---|
| **Treatment-emergent adverse events (TEAEs)[a]** | 36 (67.9)[b] | 17 (63.0) |
| Grade ≥3 | 2 (3.8)[c] | 2 (7.4) |
| **Treatment-related TEAEs[a]** | 6 (11.3)[d] | 0 |
| Grade ≥3 | 0 | 0 |
| **Serious TEAEs** | 0 | 1 (3.7)[e] |
| **TEAEs leading to study drug discontinuation** | 0 | 1 (3.7)[e] |
| **TEAEs in ≥5% of participants[f]** | | |
| Upper respiratory tract infection | 4 (7.5) | 0 |
| Sinusitis | 3 (5.7) | 1 ( 3.7) |
| COVID-19 | 1 (1.9) | 2 (7.4) |
| Diarrhea | 5 (9.4) | 1 (3.7) |
| Constipation | 3 (5.7) | 0 |

[a]Excludes ISRs. [b]45 participants (84.9%) including ISRs. [c]Acute pyelonephritis, urethritis, and kidney stone in one participant and glycosuria in another; all unrelated. [d]Lacrimation increased, nausea, device dislocation, abnormal dreams, insomnia. 36 participants (67.9%) including ISRs. [e]Metastatic pancreatic cancer. [f]≥5% of participants in either group, excluding ISRs.
**ISR,** injection site reaction; **LEN,** lenacapavir; **TAB,** teropavimab; **TEAE,** treatment-emergent adverse event; **ZAB,** zinlirvimab.

# Injection Site Reactions and Infusion Related Reactions




- ISRs[a] related to SC LEN occurred in 33 (62.3%) participants
  - Grade 1: 29 (54.7%) participants
  - Grade 2: 4 (7.5%) participants
  - Grade ≥3: 0
- No participants discontinued due to ISRs

**There were no infusion-related reactions to TAB or ZAB**

Figure reports ISRs occurring in >10% of participants.
[a]Following Day 1 SC injection.
**ISR,** injection site reaction; **LEN,** lenacapavir; **SC,** subcutaneous; **TAB,** teropavimab; **ZAB,** zinlirvimab.

# Conclusions

- In people living with HIV-1 highly susceptible to both bNAbs, the efficacy of switching to the long-acting combination of Q6M LEN, TAB, and ZAB was consistent with continuing oral standard of care
  - 96% of participants receiving LEN, TAB, and ZAB maintained virologic suppression at Week 26
- There were no infusion-related reactions to TAB or ZAB
- Up to Week 26, ADAs did not impact PK and safety
- The most common AEs were expected ISRs related to SC LEN injection; most were Grade 1
- These data support continued investigation of LEN, TAB, and ZAB as the first complete twice-yearly combination treatment for people with HIV-1
  - Upcoming analyses will evaluate secondary endpoints of longer-term efficacy and safety at Week 52, along with patient-reported outcomes

**ADAs,** anti-drug antibodies; **AE,** adverse event; **bNAbs**, broadly neutralizing antibodies; **ISR,** injection site reaction; **LEN,** lenacapavir; **PK,** pharmacokinetics; **Q6M**, every 6 months; **SC**, subcutaneous; **TAB**, teropavimab; **ZAB**, zinlirvimab.

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