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Efficacy and Safety of a Twice-Yearly Regimen of Lenacapavir, Teropavimab, and Zinlirvimab: Phase 2 Week 52 Results

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Disclosures

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Background

- Antiretroviral therapy (ART) with less frequent dosing may offer advantages over daily oral options for some people with HIV-1, such as improved adherence and reduced pill burden[1]
- Lenacapavir (LEN), the first-in-class HIV-1 capsid inhibitor, is approved for the treatment of multidrug-resistant HIV-1 in the UK, EU, US, Canada, and other countries, and can be administered subcutaneously twice yearly[2–5]
- Teropavimab (TAB; 3BNC117-LS) and zinlirvimab (ZAB; 10-1074-LS), broadly neutralizing antibodies (bNAbs) that target the HIV envelope, can also be dosed twice yearly[6]
  - TAB targets the CD4-binding site of gp120 while ZAB targets the V3 glycan on the HIV-1 envelope
- In this Phase 2 study (NCT05729568) of the combination of LEN, TAB, and ZAB, 96% of participants maintained virologic suppression at Week 26[7]

Objective: To evaluate the 1-year efficacy and safety of switching to twice-yearly LEN, TAB, and ZAB versus continuing stable baseline daily oral ART

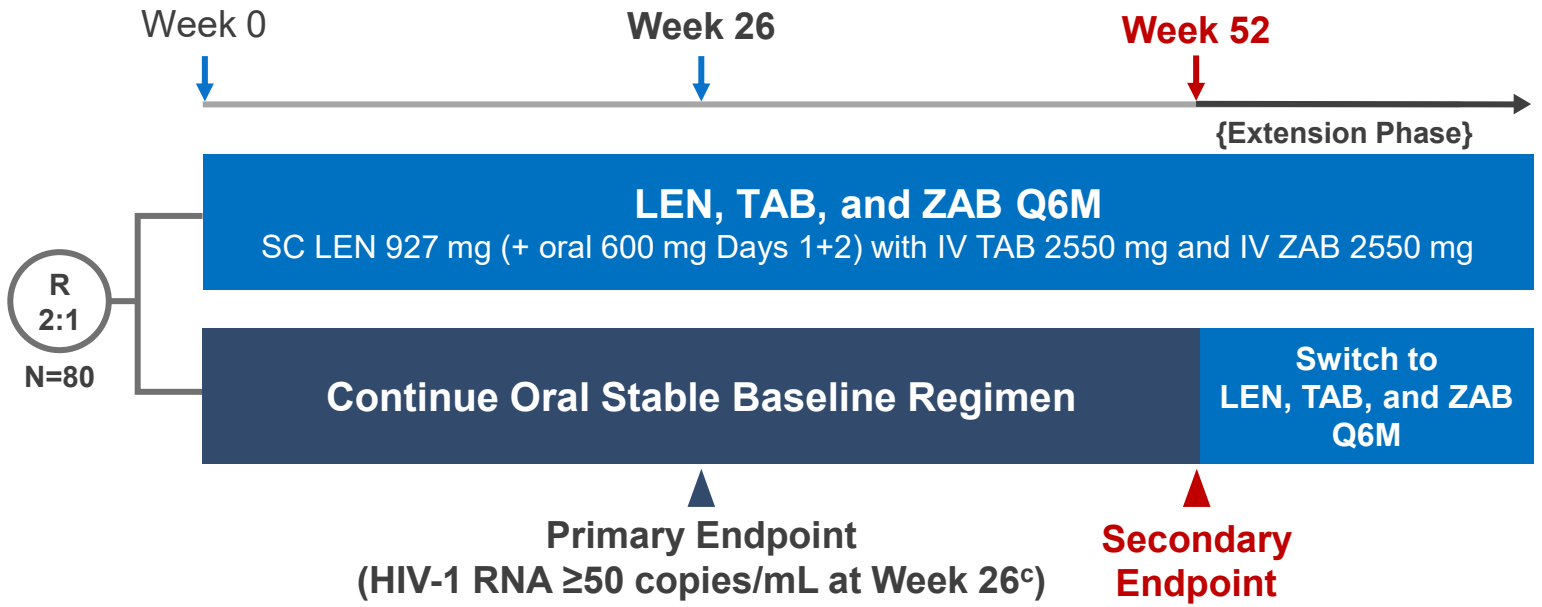
1. Claborn KR, et al. *Psychol Health Med* 2015; 20(3): 255-65. **2.** Sunlenca® UK Prescribing Information, available at https://www.medicines.org.uk/emc/files/pil.14102.pdf [Accessed October 2025]. **3.** Sunlenca® EU Summary of Product Characteristics, available at https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf [Accessed October 2025]. **4.** Sunlenca® US Prescribing Information, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf [Accessed October 2025]. **5.** Sunlenca® Canada Product Monograph, available at https://pdf.hres.ca/dpd_pm/00081120.PDF [Accessed October 2025]. **6.** Gautam R, et al. *Nat Med*. 2018;24:610–6. **7.** Ogbuagu O, et al. CROI 2025. Presentation #151.
ART, antiretroviral therapy; **bNAb,** broadly neutralizing antibody; **LEN,** lenacapavir; **TAB**, teropavimab; **ZAB,** zinlirvimab.

Phase 2 Study Design

— Randomised, open-label, active-controlled, multicenter study[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]



Week 52 Secondary Outcomes:

— HIV-1 RNA <50 copies/mL and ≥50 copies/mL[c]

— Change from baseline in CD4+ T-cell count; safety (adverse events); pharmacokinetics of LEN, TAB, and ZAB; anti-drug antibodies (ADAs)

[a]NCT05729568. [b]By PhenoSense® mAb Assay (Monogram Biosciences). [c]Per FDA snapshot algorithm.
ADA, anti-drug antibody; **ART,** antiretroviral therapy; **bNAb,** broadly neutralizing antibody; **HBV,** hepatitis B virus; **IC_{90},** 90% inhibitory concentration; **IV,** intravenous; **LEN,** lenacapavir; **Q6M,** every 6 months; **R,** randomized; **SC,** subcutaneous; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Participant Disposition and bNAb Susceptibility

Screened (N=241)
Randomized and dosed (N=80)[a]

LEN, TAB, and ZAB
Dosing Period 1: D1 to W26
n=53

Discontinued study treatment prior to W26
- *n=1; Relocated (moved cities)*

Discontinued study treatment at W26
- *n=2; Participant decision*
- *n=1; Lack of efficacy*

Dosing Period 2: W26 to W52
n=49

Completed Study Treatment to W52
n=49

Continue Oral Stable Baseline Regimen
n=27

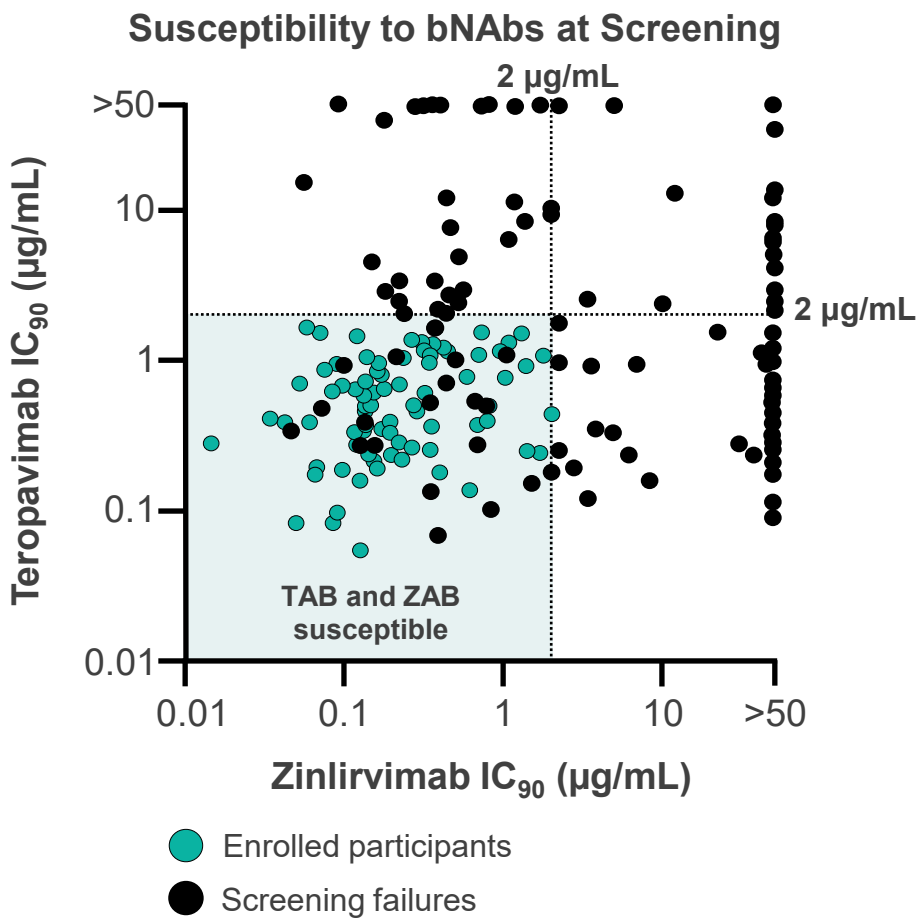
Discontinued study
- *n=1; Adverse event (metastatic pancreatic carcinoma)*

Completed Study Treatment to W26
n=26

Discontinued study treatment
- *n=1; Participant decision*

Completed Study Treatment to W52
n=25

Susceptibility results (n=200)[b]
Susceptible to TAB and ZAB (n=99)[c]



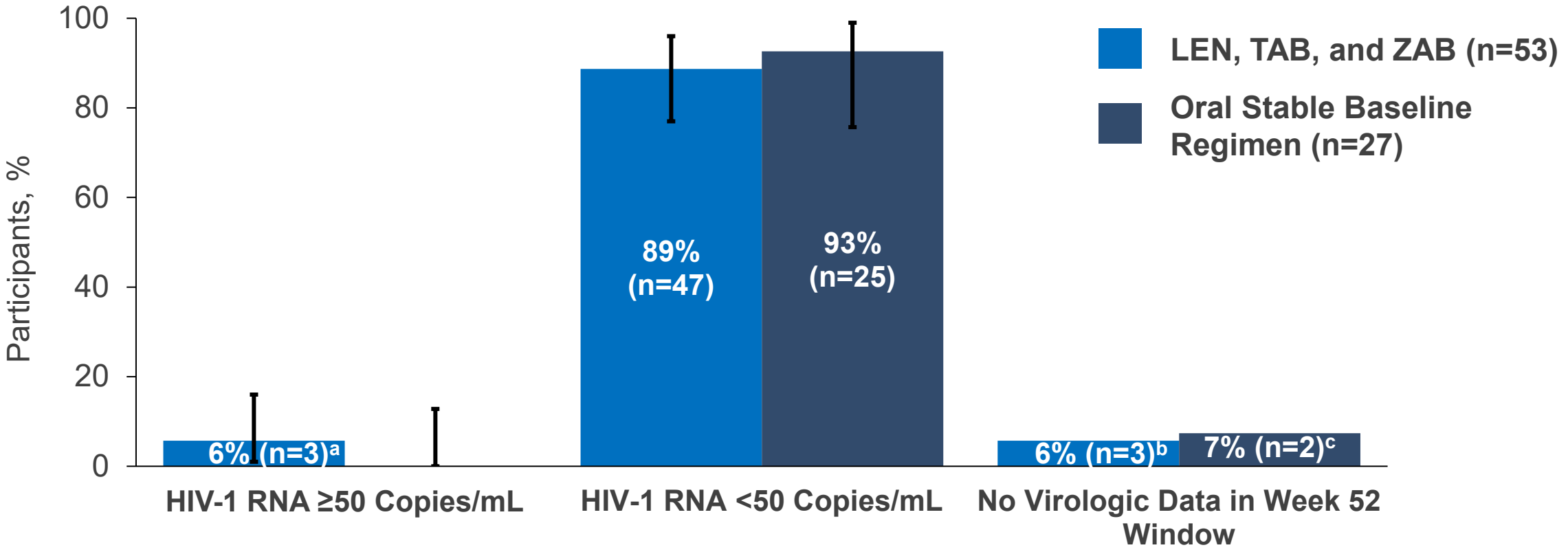
[a]84 participants met all eligibility criteria; 1 eligible but not randomized (participant decision); 3 randomized but not dosed (participant decision). [b]41 with assay failure; [c]TAB only: 47 (24%); ZAB only: 31 (16%); neither: 23 (12%).
bNAb, broadly neutralizing antibody; **D,** day; **IC_{90},** 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 (range) BMI, kg/m^2	29.2 (20.4–48.9)	29.2 (19.1–51.4)
BMI ≥30 kg/m^2, n (%)	23 (43)	9 (33)
Median (IQR) CD4+ T-cell count, cells/μL	710 (552–895)	738 (583–869)
Median (IQR) duration of all prior ARVs (years)[a]	12.2 (7.5–16.5)	16.4 (10.4–23.4)
Baseline ARV containing INSTI + NRTI, n (%)	42 (79)	23 (85)
USA region,[b] n (%)	48 (91)	19 (70)

[a]These durations are estimates based on self-reported data.
[b]Ex-USA regions include Australia, Canada, and Puerto Rico. Participants were enrolled across 34 sites.
ARV, antiretroviral; **BMI,** body mass index; **INSTI,** integrase strand transfer inhibitor; **IQR,** interquartile range; **LEN**, lenacapavir; **NRTI,** nucleoside reverse transcriptase inhibitor; **TAB,** teropavimab; **ZAB**, zinlirvimab.

Week 52 Virologic Outcomes (FDA Snapshot Algorithm)



— Median (IQR) CD4+ T-cell count increased from baseline at Week 52:

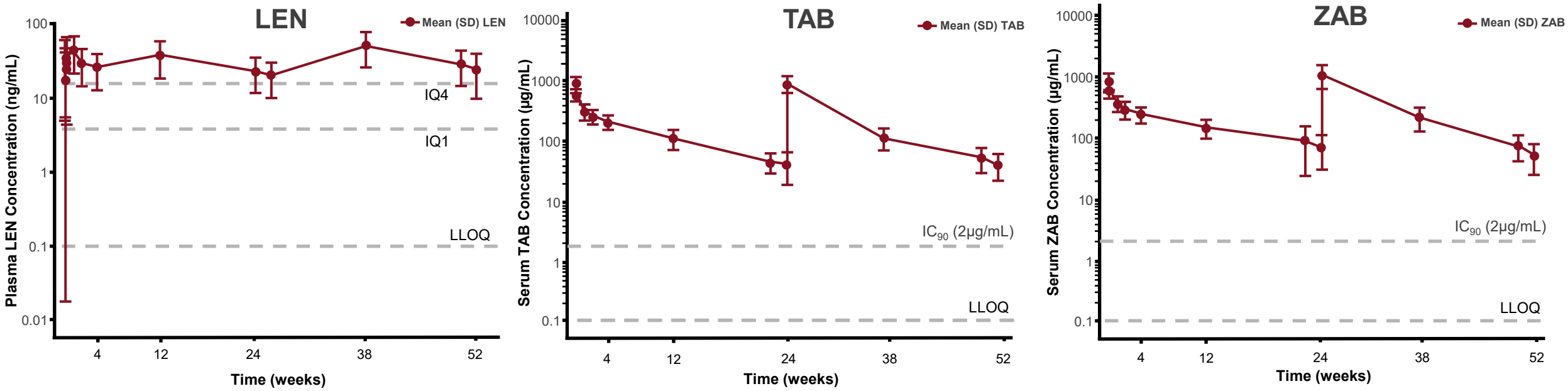
- +32 (–43 to 119) cells/µl in the LEN, TAB, and ZAB group
- +38 (–30 to 146) cells/µl in the oral stable baseline regimen group

[a]n=2 with HIV-1 RNA ≥50 copies/mL in W52 window, n=1 with HIV-1 RNA ≥50 copies/mL discontinued study drug due to lack of efficacy at W26. All 3 participants restarted standard first-line oral ART (B/F/TAF) and resuppressed in follow-up. [b]n=3 discontinued study drug due to participant decision with last HIV-1 RNA <50 copies/mL. [c]n=1 discontinued study drug due to participant decision and n=1 discontinued study drug due to adverse event, both with last HIV-1 RNA <50 copies/mL.

ART, antiretroviral therapy; **IQR,** interquartile range; **LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Pharmacokinetics and Anti-Drug Antibodies

- Mean concentrations of LEN, TAB, and ZAB were maintained through Week 52



- Treatment-emergent ADAs against: TAB, n=6 (11%); ZAB, n=9 (17%)
- PK profiles of participants with and without ADAs were similar; ADAs were not associated with adverse events or virologic rebound
- Further PK and ADA data will be presented at IDWeek 2025 (Poster P-1248)

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

Safety Overview (Excluding ISRs related to SC LEN)

Participants, n (%)	LEN, TAB, and ZAB n=53	Oral Stable Baseline Regimen n=27
AEs	40 (76)[a]	21 (78)
Grade ≥3	4 (8)[b]	2 (7)
Treatment-related AEs	5 (9)[c]	0
Grade ≥3	0	0
Serious AEs	1 (2)[d]	1 (4)[e]
AEs leading to study drug discontinuation	0	1 (4)[e]
AEs in ≥5% of participants[f]		
Diarrhea	7 (13)	1 (4)
Upper respiratory tract infection	5 (9)	0
COVID-19	3 (6)	2 (7)
Viral upper respiratory tract infection	3 (6)	1 (4)
Sinusitis	3 (6)	1 (4)
Constipation	3 (6)	0
Nausea	3 (6)	1 (4)
Hemorrhoids	3 (6)	1 (4)
Cough	3 (6)	0

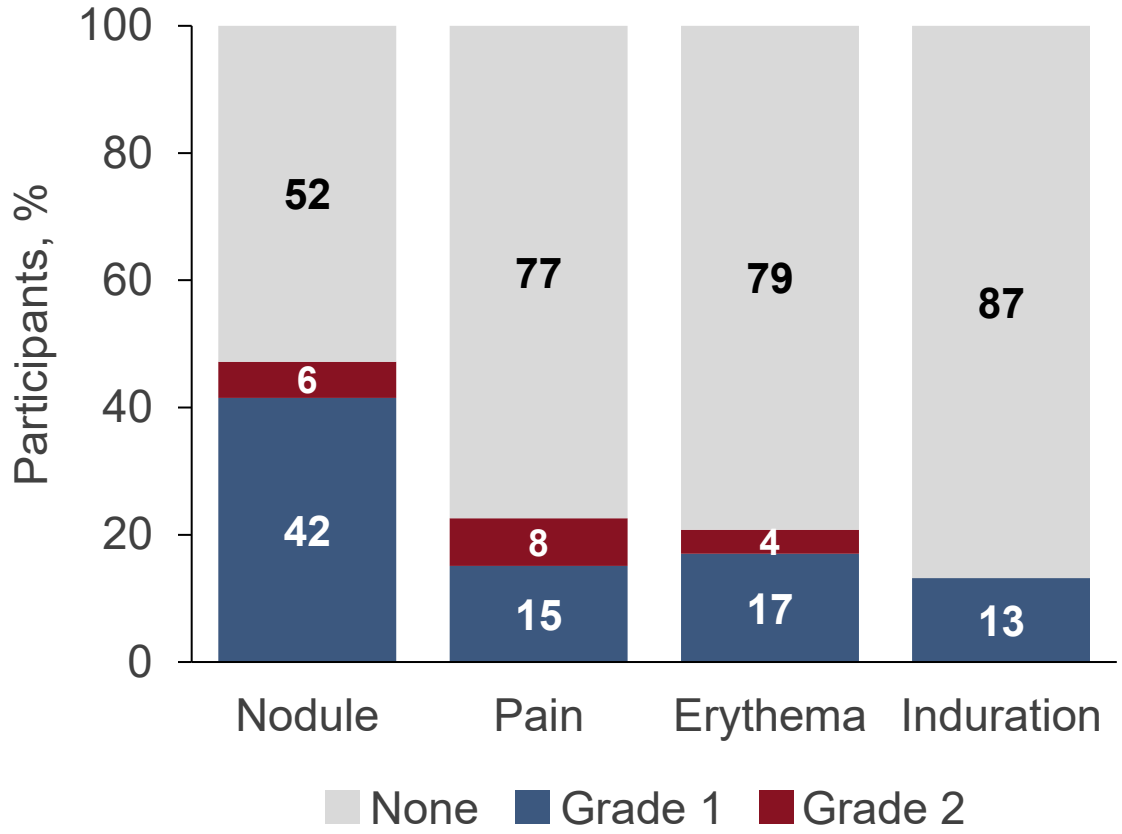
Safety data through the Week 52 data cut (up to last participant Week 52 visit) were included. [a]47 participants (89%) including ISRs. [b]Perineal abscess, acute pyelonephritis, scrotal abscess, ureteritis, abnormal weight loss, glycosuria, and nephrolithiasis in four participants. [c]Lacrimation increased, nausea, device dislocation, abnormal dreams, and insomnia in 5 participants. 37 participants (70%) including ISRs. [d]Perineal abscess and scrotal abscess in one participant. [e]Metastatic pancreatic carcinoma in one participant. [f]≥5% of participants in either group, excluding ISRs.
AE, adverse event; **ISR,** injection site reaction; **LEN,** lenacapavir; **SC**, subcutaneous; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Injection Site Reactions and Infusion-Related Reactions

- The most common AEs were Grade 1 or 2 ISRs related to SC LEN in 36 (68%) participants[a]
  - Grade 1: 30 (57%) participants
  - Grade 2: 6 (11%) participants
- No participants discontinued due to ISRs

There were no infusion-related reactions to TAB or ZAB

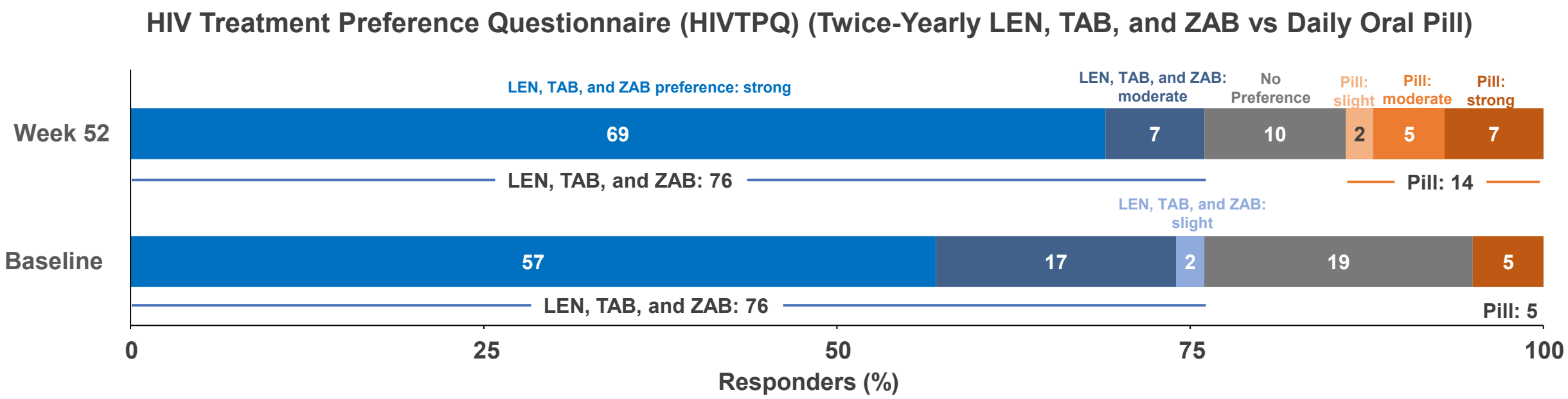
Injection Site Reactions Related to SC LEN Occurring in ≥10% of Participants Receiving LEN, TAB, and ZAB



[a]Participants who received one or both SC injections at Day 1 or Week 26.

AE, adverse event; **ISR,** injection site reaction; **LEN,** lenacapavir; **SC,** subcutaneous; **TAB,** teropavimab; **ZAB,** zinlirvimab.

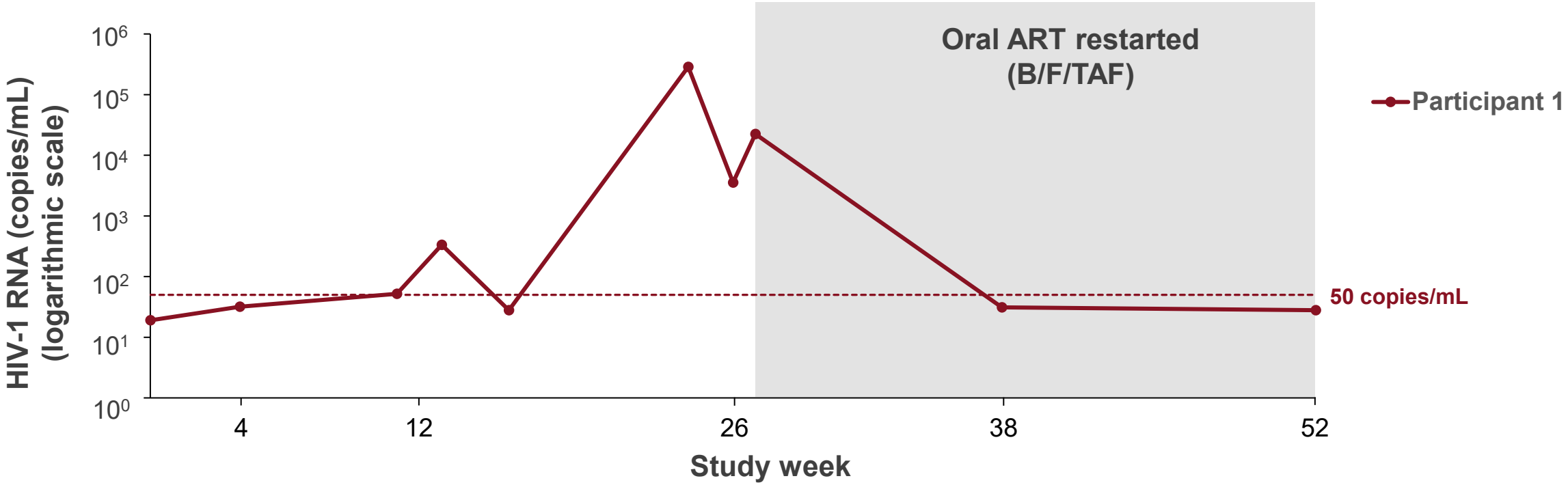
Patient-Reported Outcomes



- Overall, 42/53 participants completed the HIVTPQ at baseline, Week 26, and Week 52
- At Week 52, 32/42 (76%) participants **preferred LEN, TAB, and ZAB** (strong, n=29; moderate, n=3) over daily oral ART
- At Week 52, 38/42 (90%) participants indicated **twice-yearly LEN, TAB, and ZAB would be easier to adhere to** compared to daily oral ART

HIV Treatment Satisfaction Questionnaire (Status) scores in the LEN, TAB, and ZAB group increased from baseline to Week 52.
HIV Dependent Quality of Life Questionnaire scores in the LEN, TAB, and ZAB group improved from baseline to Week 52.
ART, antiretroviral therapy; **LEN,** lenacapavir; **HIVTPQ,** HIV Treatment Preference Questionnaire; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Participants with Virologic Rebound: Participant 1



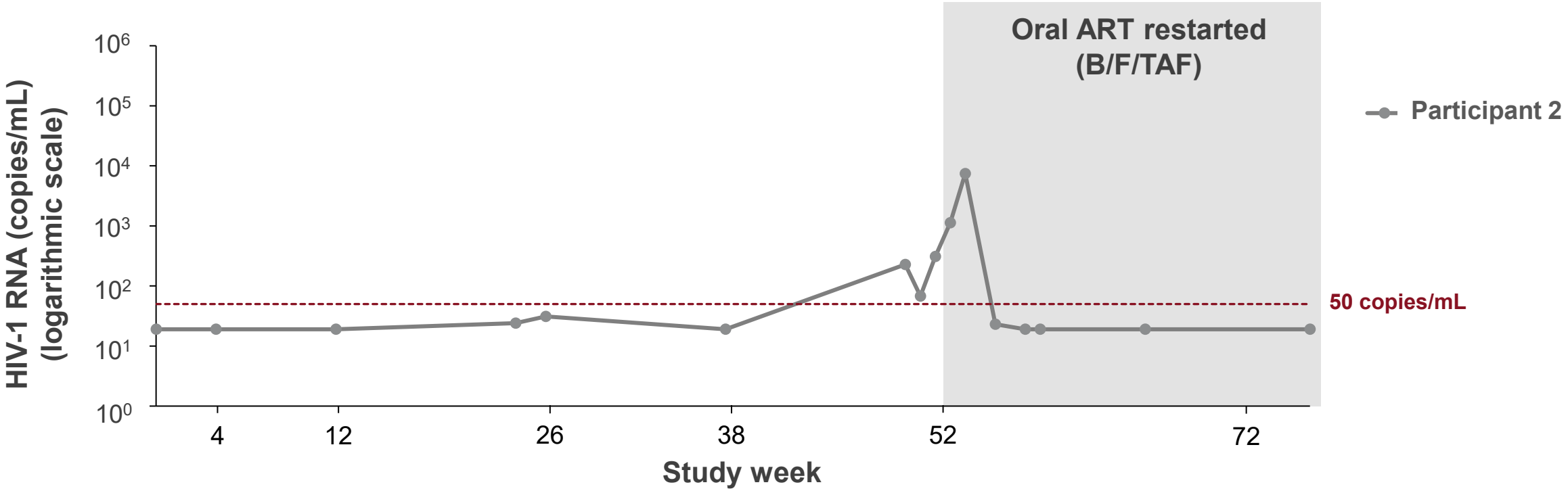
- Week 12: Upper respiratory tract infection and steroid usage
- Week 24: Developed resistance to LEN and lost susceptibility to ZAB[a]
- No ADAs to TAB or ZAB

Confirmed virologic rebound: HIV-1 RNA ≥50 copies/mL, confirmed at the following visit. Week 12 virologic rebound was confirmed in the setting of viral upper respiratory tract infection (Weeks 11–14) and steroid usage (methylprednisolone Weeks 12–13). Virologic failure was confirmed at Week 24 following Grade 1 sinusitis at Weeks 19–20 (treated with Amox-Clav).

1. Ogbuagu O, et al. CROI 2025. Presentation #151. [a]Developed resistance to LEN (Q67H in capsid) and lost susceptibility to ZAB (IC_{90}>50 µg/mL).

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

Participants with Virologic Rebound: Participant 2



— Week 50: Lost susceptibility to ZAB (genotype only)

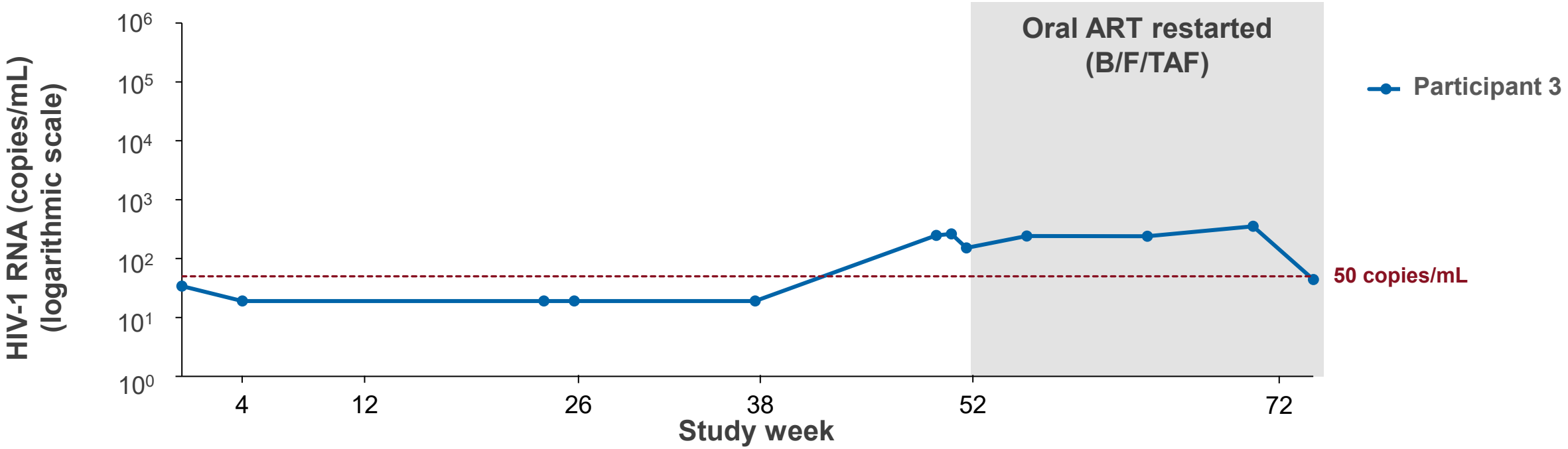
— No ADAs to TAB or ZAB

Confirmed virologic rebound: HIV-1 RNA ≥50 copies/mL, confirmed at the following visit.

ADA, antidrug antibody; **ART**, antiretroviral therapy; **B/F/TAF,** bictegravir/emtricitabine/tenofovir alafenamide; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Note: Voiceover to note the actual viral load before the switch to oral ART (for all 3 ppts)

Participants with Virologic Rebound: Participant 3



- Low level viremia persisted post-ART restart, with peak viral load at Week 71 (353 copies/mL)
- No evidence of HIV-1 resistance mutations in rebounding virus; post-hoc analysis of HIV-1 RNA showed identical sequences
- No resistance detected
- First ADAs to TAB detected at Week 26 and persistent at Weeks 38 and 52; ADAs to ZAB first detected at Week 12 and persistent to Week 26
  - ADAs did not impact PK

Confirmed virologic rebound: HIV-1 RNA ≥50 copies/mL, confirmed at the following visit.

ADA, antidrug antibody; **ART**, antiretroviral therapy; **B/F/TAF,** bictegravir/emtricitabine/tenofovir alafenamide; **PK,** pharmacokinetics; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Assessment of Virologic Rebound Through Week 52

- The three participants with confirmed virologic rebound were male, had HIV-1 sub-type B, had antibody trough concentrations mostly in the lowest quartile, and confirmed virologic failure late in the dosing interval

	Participant 1	Participant 2	Participant 3
Baseline BMI, kg/m^2	30.8	38.3	36.3
Baseline weight, kg	109	143	118
Time of rebound	Week 24	Week 50	Week 50
LEN trough PK	4th percentile	13th percentile	66th percentile
TAB trough PK	25th percentile	18th percentile	12th percentile
ZAB trough PK	37th percentile	18th percentile	6th percentile
Baseline susceptibility TAB IC_{90}, µg/mL	1.53	0.08	0.36
Baseline susceptibility ZAB IC_{90}, µg/mL	0.72	0.09	0.17

- Weight is a clinically significant covariate that affects antibody exposure, as identified in preliminary TAB and ZAB PopPK models
  - All three virologic rebound participants weighed >100kg, with lower bNAb exposures
- Data are not sufficient to establish a statistical association between TAB and ZAB exposures and risk of virologic rebound

All eligible study participants were highly susceptible to both bNAbs (IC_{90} ≤2 µg/mL) at study start.
BMI, body mass index; **bNAb,** broady neutralizing antibody; **IC_{90},** 90% inhibitory concentration; **LEN,** lenacapavir; **PK,** pharmacokinetics; **PopPK,** population pharmacokinetic; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Conclusions

- Overall, 89% of participants receiving LEN, TAB, and ZAB remained suppressed at Week 52 by FDA Snapshot Algorithm
  - Efficacy of LEN, TAB, and ZAB was similar to standard-of-care daily oral ART
  - Three participants met confirmed virologic rebound criteria; two had emergent resistance (one each to LEN and ZAB) and one had low level viremia that persisted on oral therapy with no emergent resistance
  - All three participants suppressed on oral therapy
  - The relationship between viral rebound and PK is being explored
- Through Week 52, LEN, TAB, and ZAB was well tolerated
- The majority of participants having experienced both modalities of treatment preferred LEN, TAB, and ZAB over daily oral ART through Week 52
- These data support further evaluation of LEN, TAB, and ZAB in Phase 3 studies
- This long-acting combination regimen has potential as the first complete twice-yearly combination treatment for people with HIV-1

AE, adverse event; **ART,** antiretroviral therapy; **ISR,** injection site reaction; **LEN,** lenacapavir; **PK,** pharmacokinetics; **SC**, subcutaneous; **TAB**, teropavimab; **ZAB**, zinlirvimab.

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