BHIVA British HIV Association

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Lenacapavir with bNAbs Teropavimab (GS-5423) and Zinlirvimab (GS-2872) Dosed Every 6 Months in People with HIV

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*Listed here for presentation purposes only

Disclosures & Acknowledgments

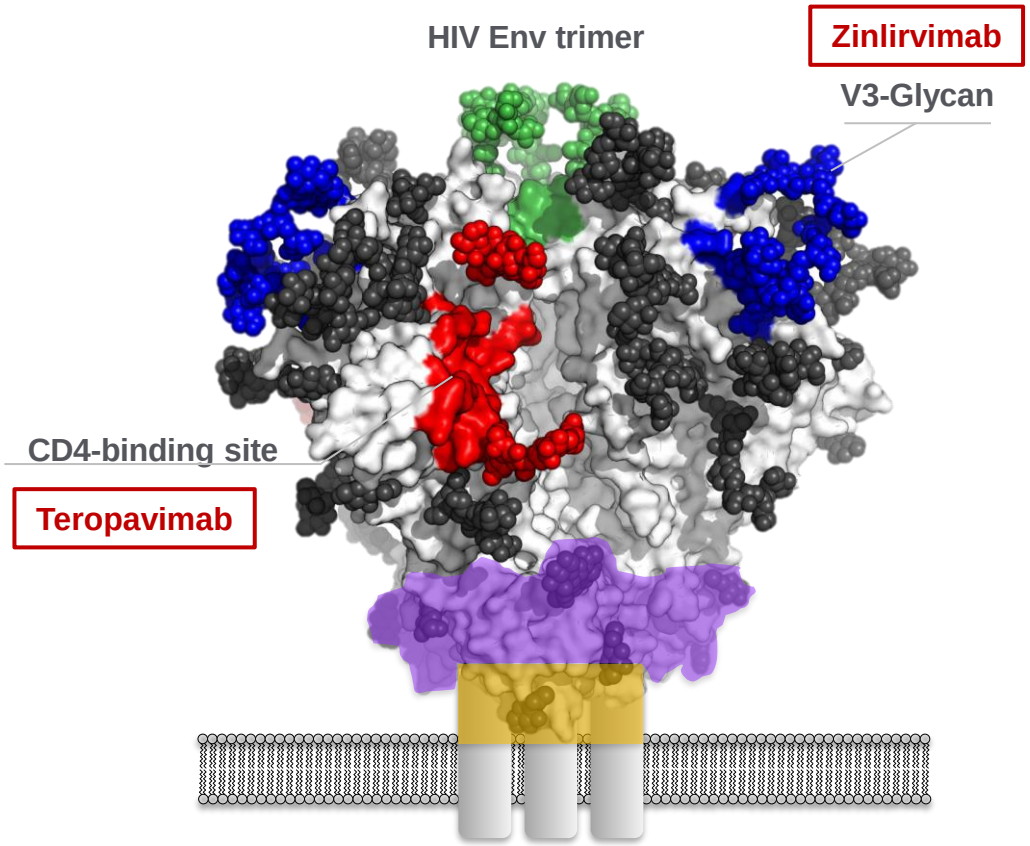
- Neal Marshall (presenting author) is a full-time employee of Gilead Sciences UK & Ireland.

- We extend our thanks to the study participants, their families, site staff, and all participating investigators.

- This study was funded by Gilead Sciences, Inc.

Background

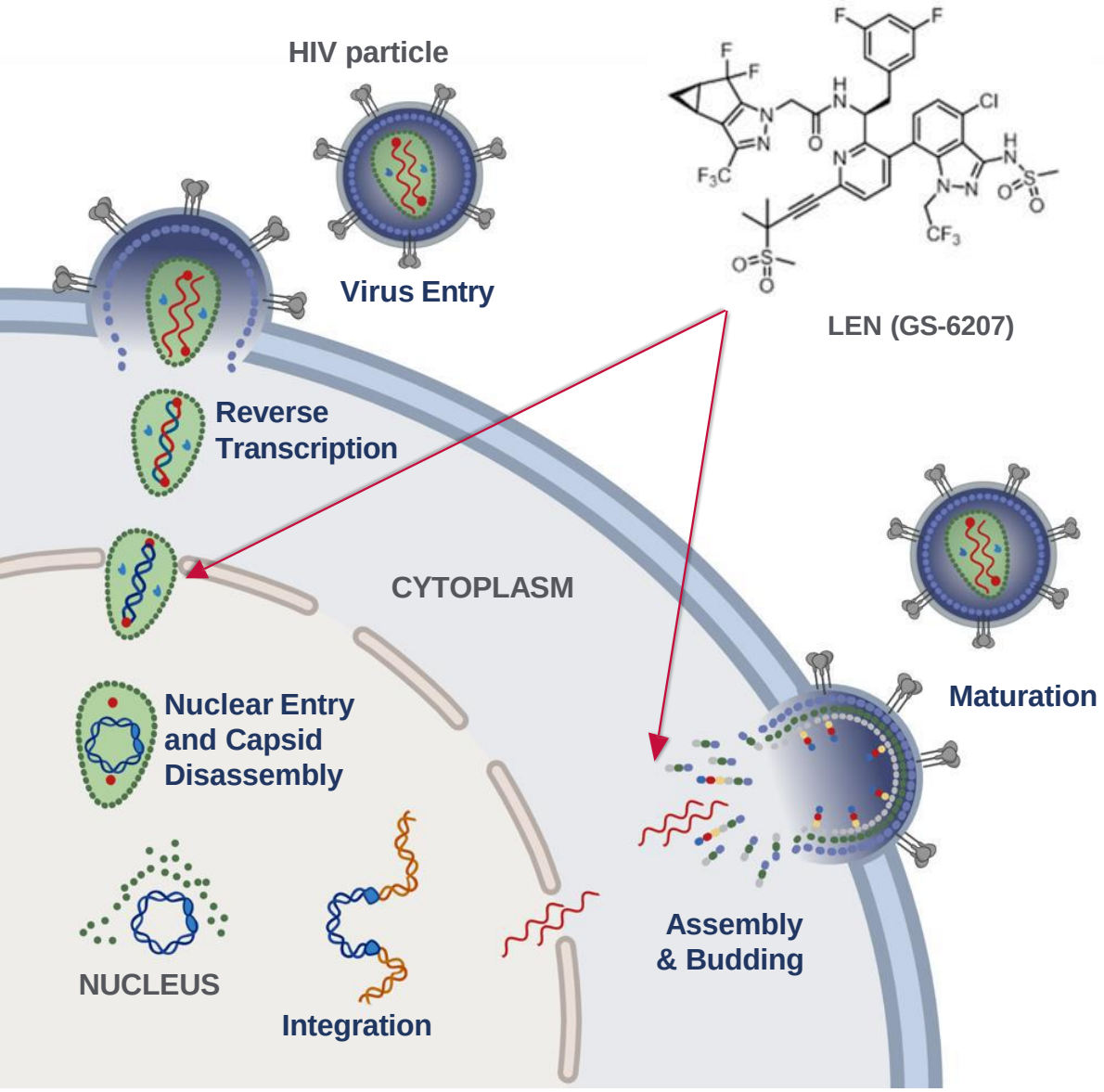
- Broadly neutralising antibodies (bNAbs) are currently in development for the prevention, treatment and as part of potential cure strategies for HIV.[1,2]
  - Teropavimab (TAB; GS-5423; 3BNC117-LS) targets the CD4-binding site of gp120 of HIV-1 Env
  - Zinlirvimab (ZAB; GS-2872; 10-1074-LS) targets a non-overlapping epitope on the V3 glycan of HIV-1 Env.
- Both antibodies were modified to extend their half-lives for long-acting therapy that may allow for dosing every 6 months.
- An estimated > 50% of clade B viruses are highly susceptible to both bNAbs and > 90% are highly susceptible to either bNAb with a 90% inhibitory concentration (IC_{90}) < 2 µg/mL.[3]



- **We hypothesize that combining TAB and ZAB with a long-acting antiviral agent could provide a complete long-acting therapeutic regimen for HIV treatment.**

[1]Caskey M, Kuritzkes DR. Clin Infect Dis. 2022 Nov 21;75(Suppl 4):S530-S540. [2]Waters L, de Miguel-Buckley R, Poulin S, Arribas JR. Clin Infect Dis. 2023 Mar 21;76(6):1136-1141.
[3]Yoon H, et al. Nucleic Acid Res. 2015 Jul 1;43(W1):W213-9.

Background (cont'd)



- Lenacapavir (LEN) is a first-in-class, small molecule capsid inhibitor with:
  - Multimodal mechanism, a long half-life and low potential for drug-drug interactions
  - Subcutaneous administration every 6 months
- LEN plus an optimised background regimen has demonstrated clinical efficacy in people with HIV who are highly treatment experienced with multidrug resistant HIV-1 taking a failing antiretroviral regimen.[1]

We investigated whether LEN in combination with TAB and ZAB can maintain HIV suppression for 6 months.

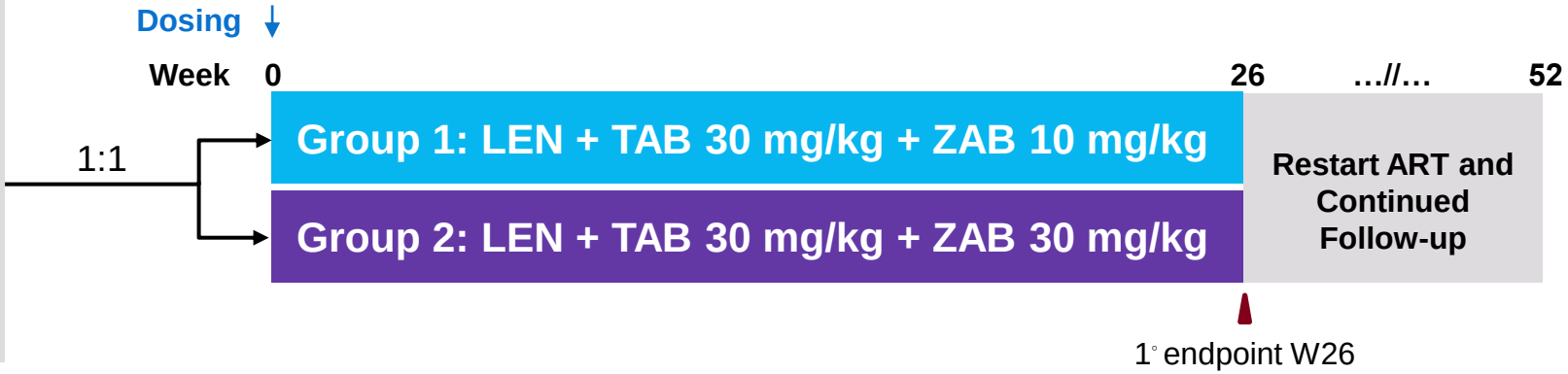
[1] Gupta SK et al. Lancet HIV. 2023 Jan;10(1):e15-e23

Study Design

- Randomised, blinded phase 1b study assessing safety profile and efficacy of a long-acting regimen LEN + TAB + ZAB administered in two different doses. (NCT04811040)

Key Inclusion Criteria

- **Adults living with HIV-1**
- **Virologically suppressed ≥ 18 months**
- **Viral susceptibility to both TAB and ZAB**
- **CD4 nadir ≥ 350**
- **CD4 at entry ≥ 500**



HIV RNA measured at least every 4 weeks until Week 26.

Primary Endpoint:

- % Experiencing treatment-emergent serious adverse events (SAEs) at week 26

Secondary Endpoints Included:

- % HIV VL< 50 copies/ml at week 26 (FDA snapshot algorithm)
- % Treatment-emergent adverse events (AEs)
- Pharmacokinetic (PK) parameters of TAB, ZAB and LEN

The study design was amended to have participants restart ART at W26 after the FDA clinical hold on investigational LEN due to stability issues in borosilicate vials[1]

[1] FDA lifts clinical hold on investigational lenacapavir for the treatment and prevention of HIV. Press release. May 16, 2022.

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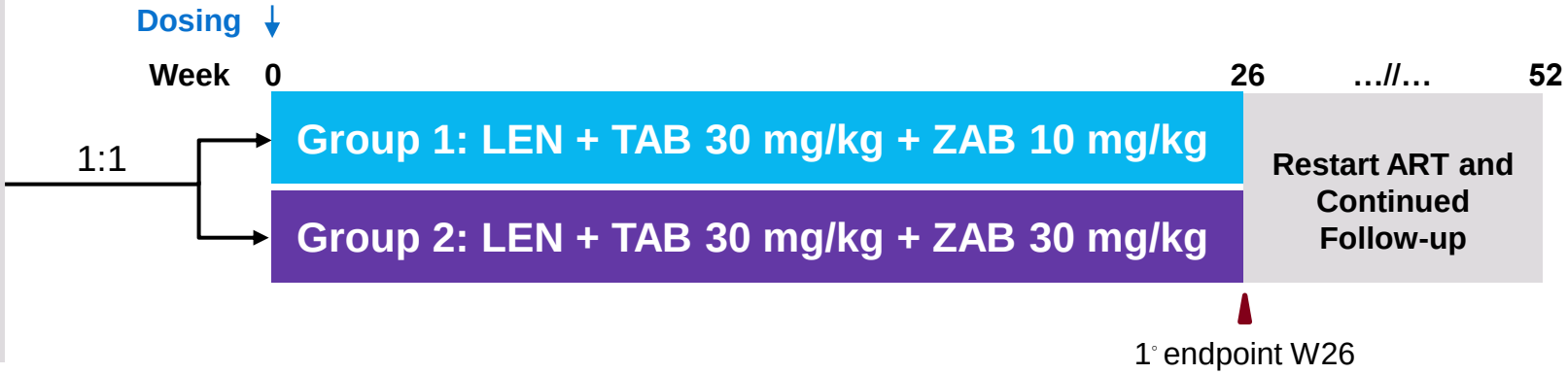

	Day 1	Day 2
LEN oral 600 mg		
LEN SC 927 mg		-
TAB IV 30 mg/kg		-
ZAB IV 10 mg/kg or 30 mg/kg		-

HIV RNA measured at least every 4 weeks until Week 26.

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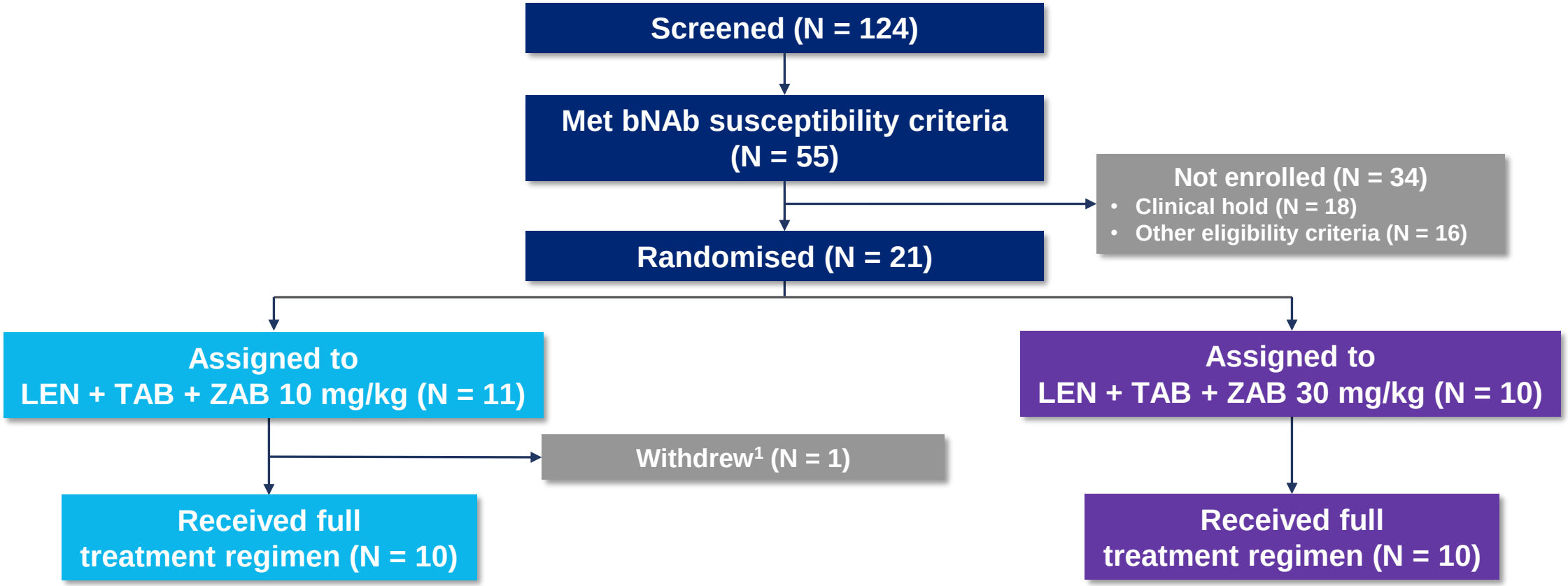
Participant Disposition



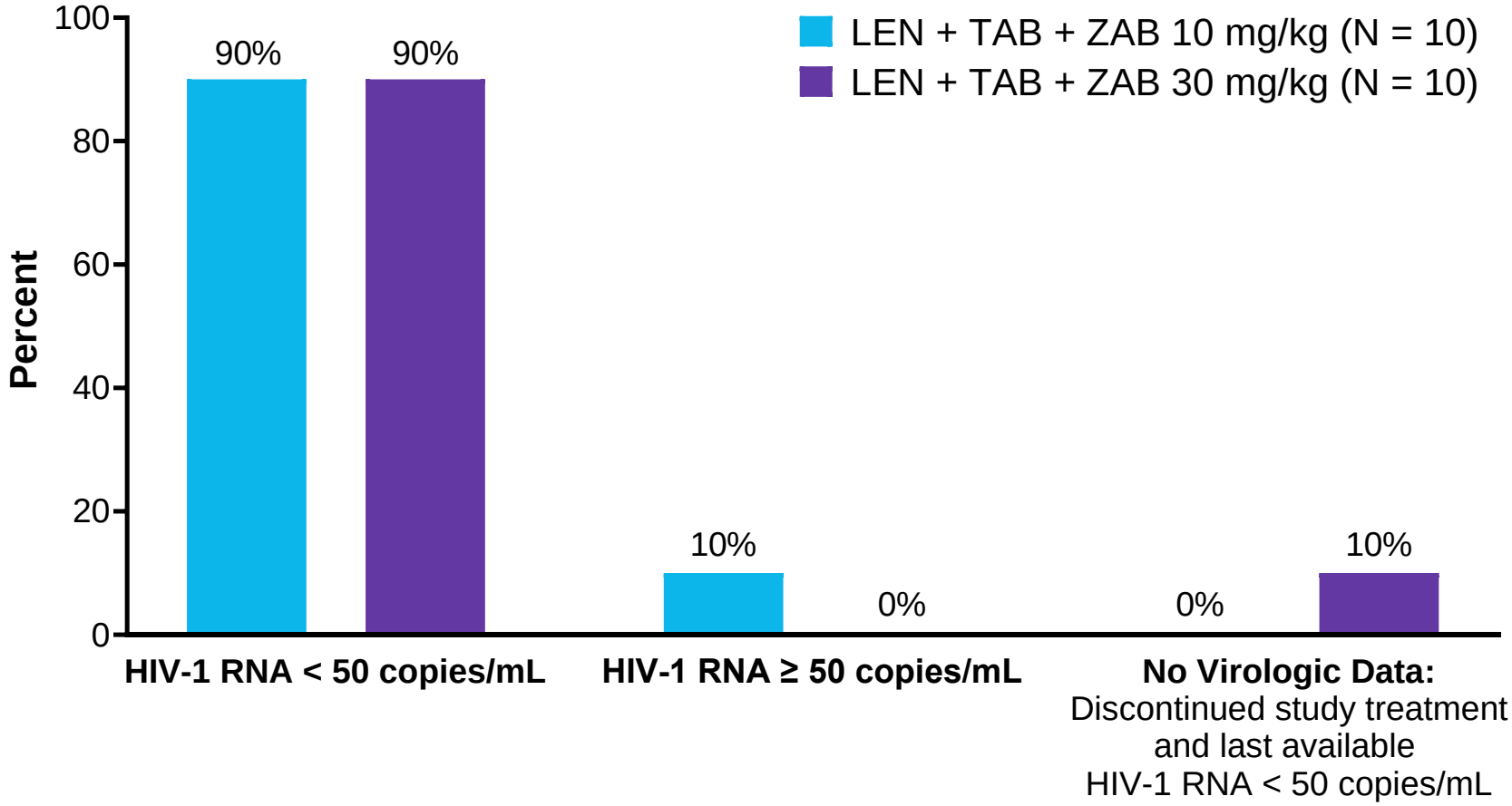
- All randomised participants were included in the safety analysis (N = 21); those who received the complete study regimens (oral LEN, SC LEN, and bNAbs) are included in the efficacy analyses (N = 20).

[1] Participant received oral LEN and then withdrew consent prior to injections or infusions; they continued their baseline ART and are included in the safety analyses.

Enrolled Participant Demographics and Baseline Characteristics

		LEN + TAB + ZAB 10 mg/kg (N = 11)	LEN + TAB + ZAB 30 mg/kg (N = 10)	Total (N = 21)
Age, median (range)		46 (31 to 61)	37 (25 to 59)	44 (25 to 61)
Sex at birth, n	Male	11	7	18
	Female	0	3	3
Race, n	Asian	2	1	3
	Black	1	2	3
	White	7	5	12
	Other	1	2	3
Hispanic or Latino ethnicity, n		4	3	7
Weight (kg), median (range)		90.2 (58.9 to 150.0)	92.9 (60.2 to 143.0)	90.2 (58.9 to 150.0)
Body mass index (kg/m^2), median (range)		30.2 (21.6 to 42.9)	30.2 (21.6 to 54.1)	30.2 (21.6 to 54.1)
CD4 cell count (per mL), median (range)		778 (547 to 1391)	1024 (667 to 1644)	909 (547 to 1644)
Duration of baseline ART regimen (years), median (range)		3.6 (2.4 to 4.8)	2.6 (2.0 to 5.5)	2.6 (2.0 to 5.5)
Time since HIV diagnosis (years), median (range)		12.4 (6.4 to 26.3)	5.3 (2.6 to 22.4)	8.2 (2.6 to 26.3)

Virologic Efficacy Outcomes at Week 26 by FDA Snapshot Algorithm



- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and resuppressed on baseline oral ART.

[1] Participant withdrew due to personal decision.

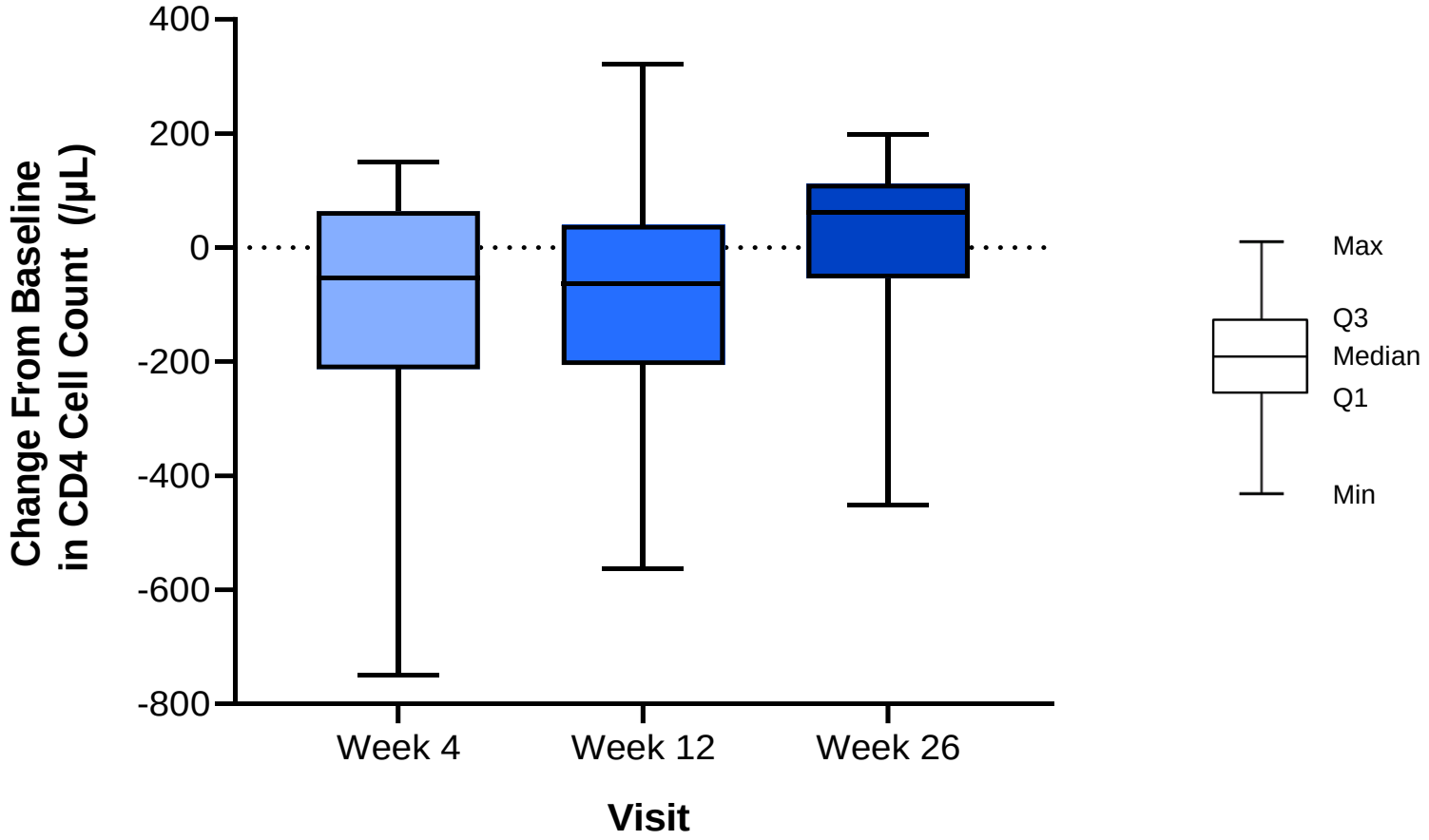
Safety Profile and Tolerability

	LEN + TAB + ZAB 10 mg/kg (N = 11)	LEN + TAB + ZAB 30 mg/kg (N = 10)	Total (N = 21)
Any adverse event (AE), n	9	10	19
AEs of any grade occurring in 3 or more study participants			
Injection-site pain, n	5	5	10
Injection-site erythema, n	4	3	7
Injection-site nodule, n	4	2	6
Injection-site induration, n	2	4	6
Injection-site mass, n	3	1	4
COVID-19, n	3	0	3
Upper respiratory tract infection, n	3	0	3

- There were no serious AEs, Grade 4 AEs, or AEs that led to study treatment discontinuation.
- There were two Grade 3 AEs:
  - One injection-site cellulitis on Day 1, resolved with antibiotics
  - One injection-site erythema on Day 3, resolved without intervention by Day 10
- One participant experienced a Grade 1 infusion-related reaction of pyrexia with flushing, which resolved without treatment.
- There were no clinically meaningful treatment-emergent lab abnormalities ≥ Grade 3.

n = number of participants.

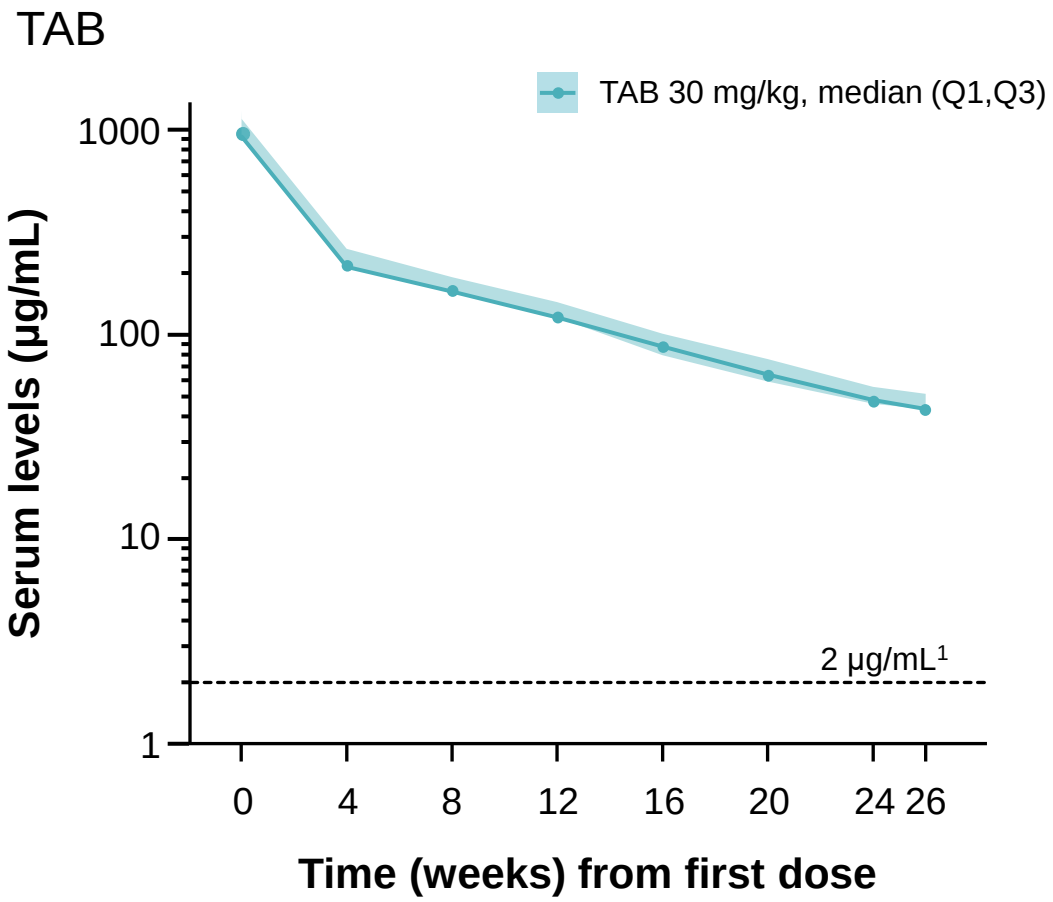
Change From Baseline by Visit in CD4 Cell Count in All Participants



Number of Participants:	20	18	18

- CD4 cell counts remained stable over the course of the study period.

Pharmacokinetics of Teropavimab, Zinlirvimab, and Lenacapavir



- Therapeutic concentrations of TAB, ZAB, and LEN were maintained through Week 26.

[1] 2 µg/mL was the level required for sensitivity in the screening assay.

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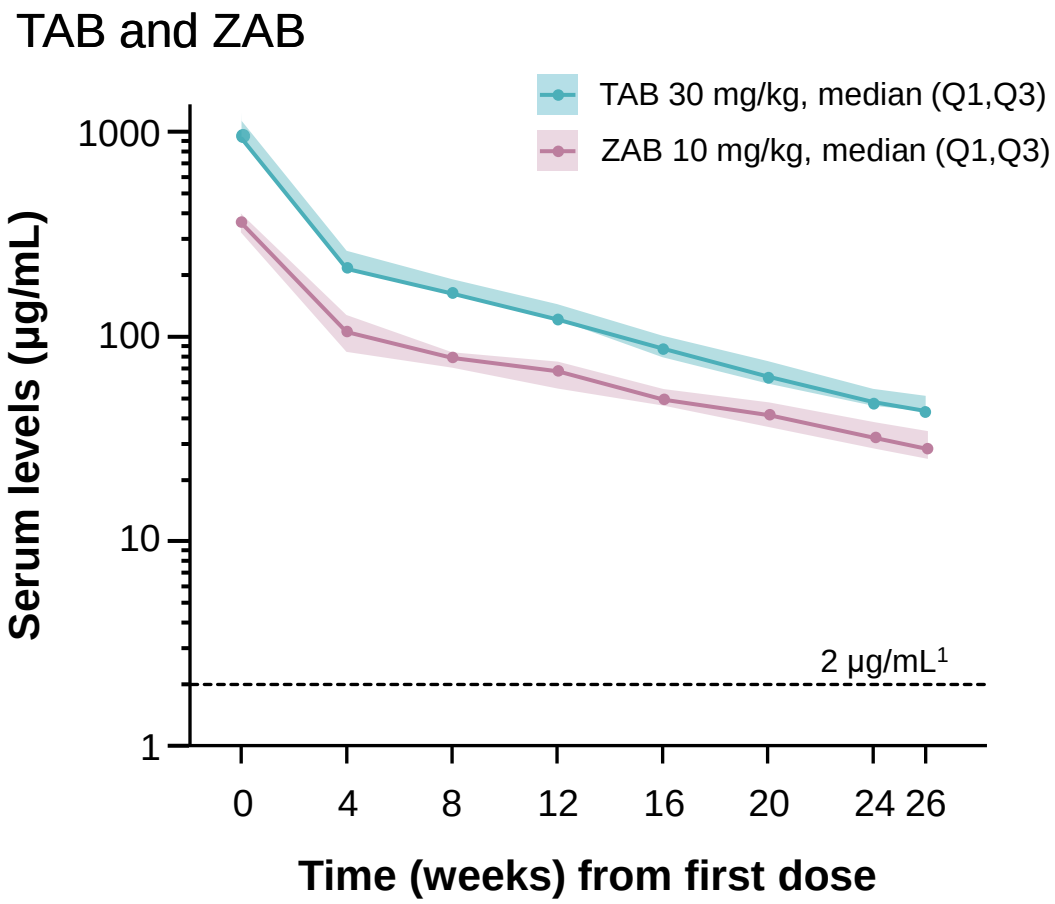

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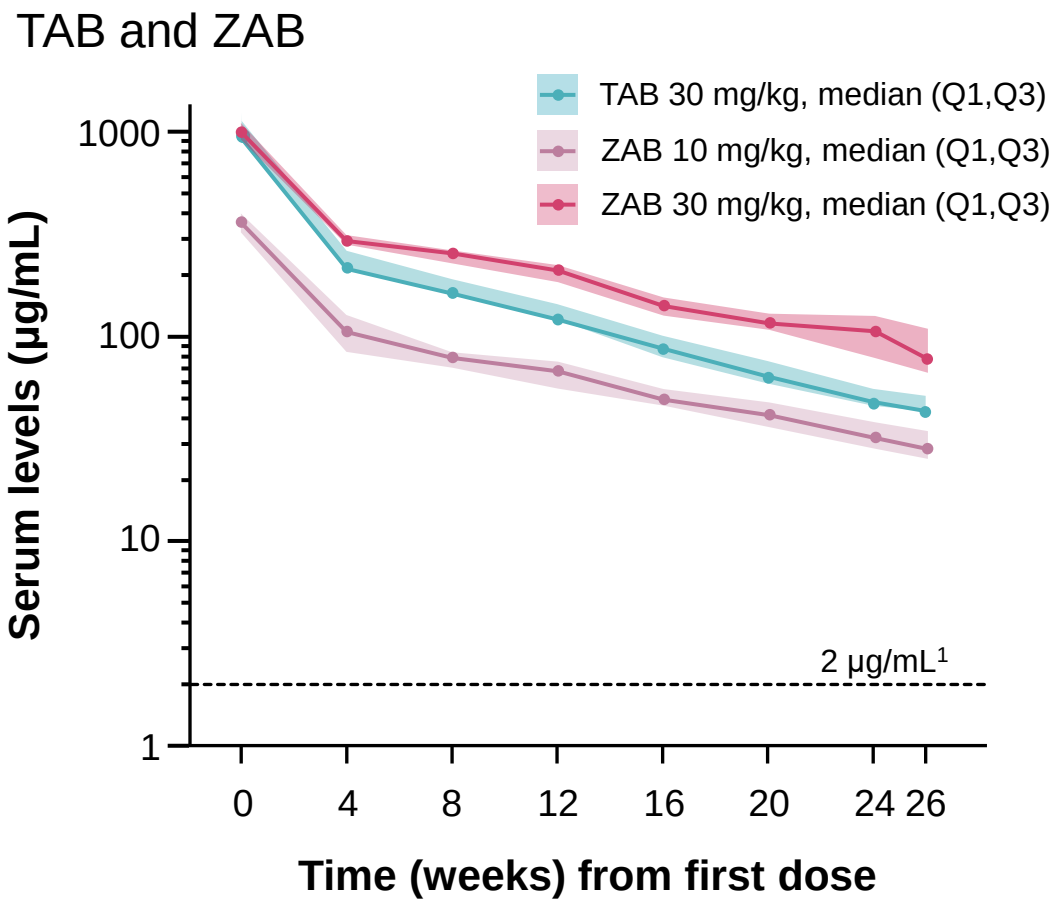

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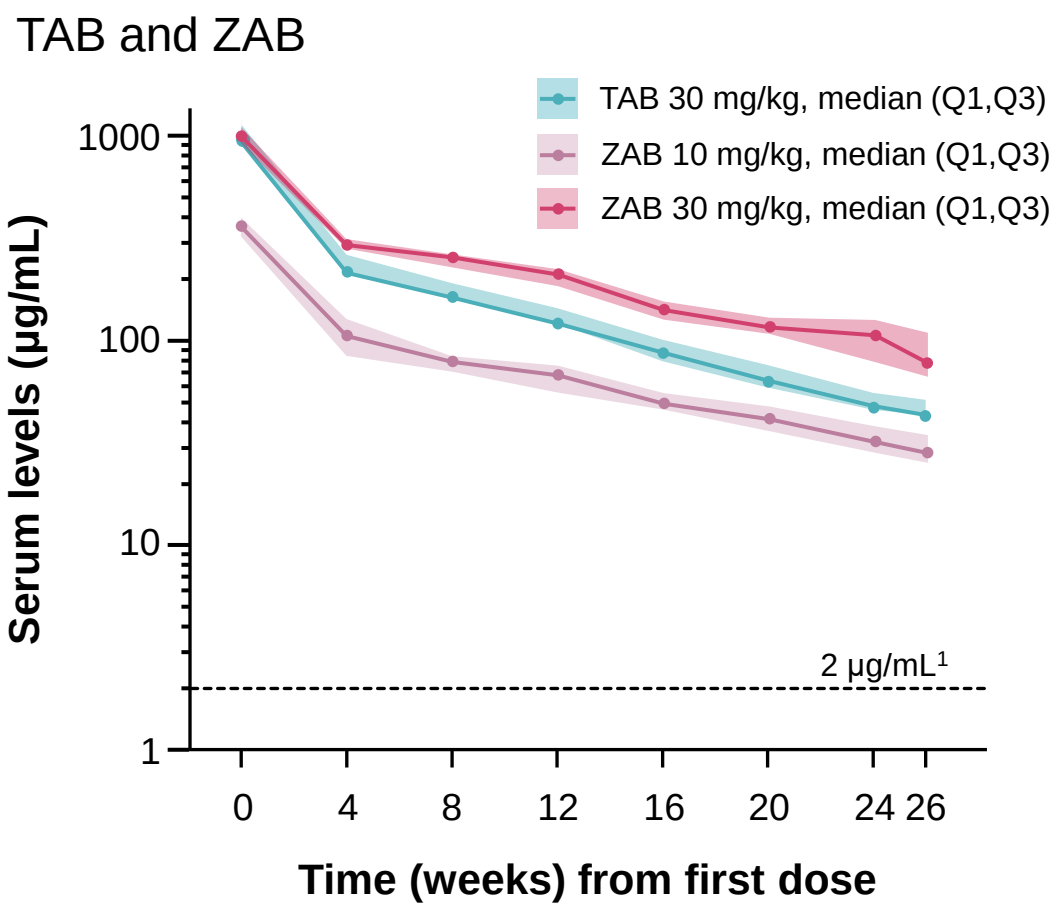

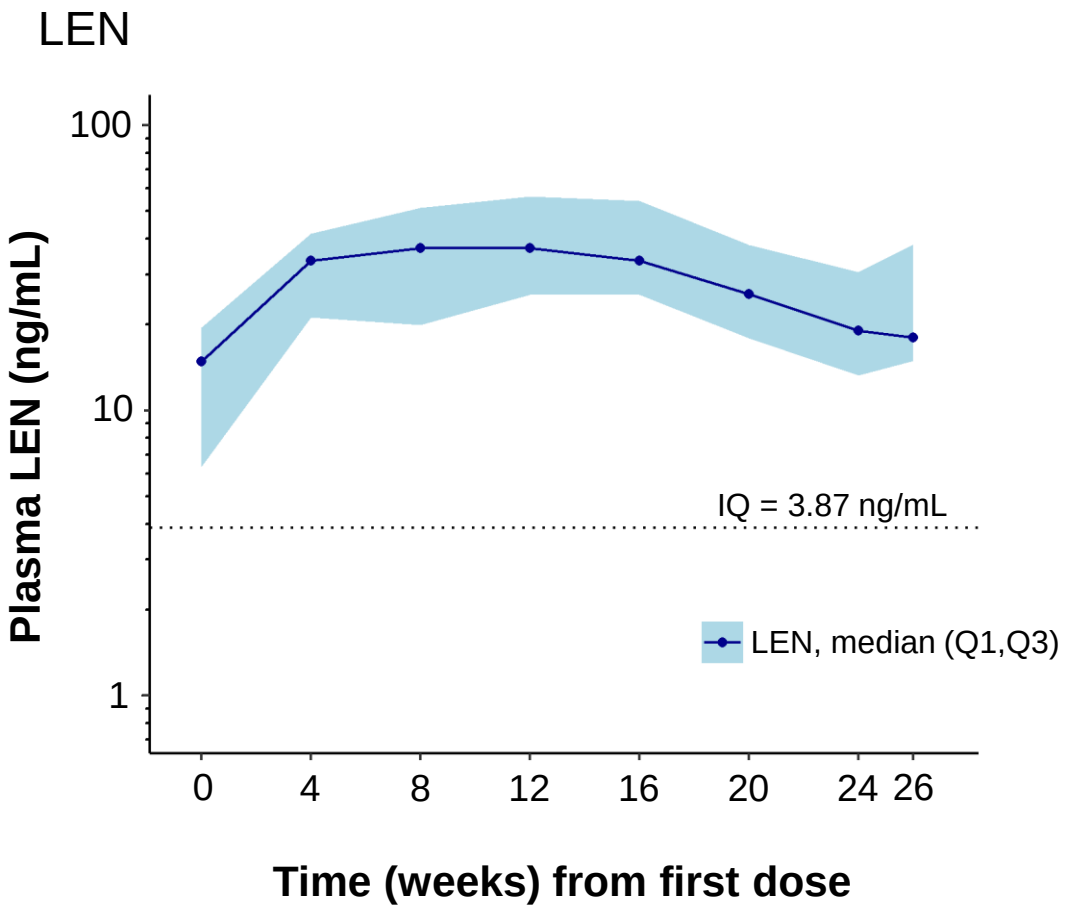

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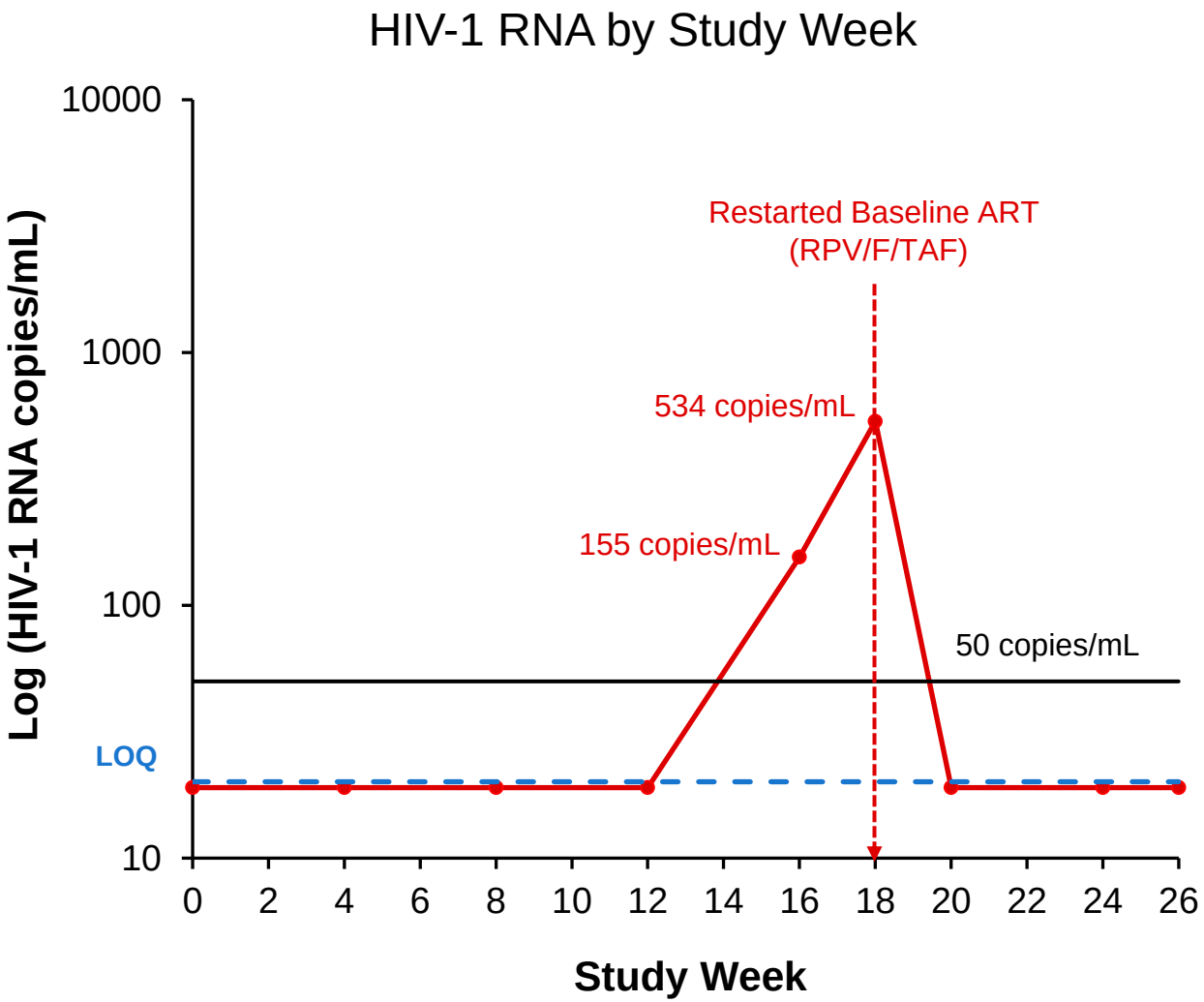
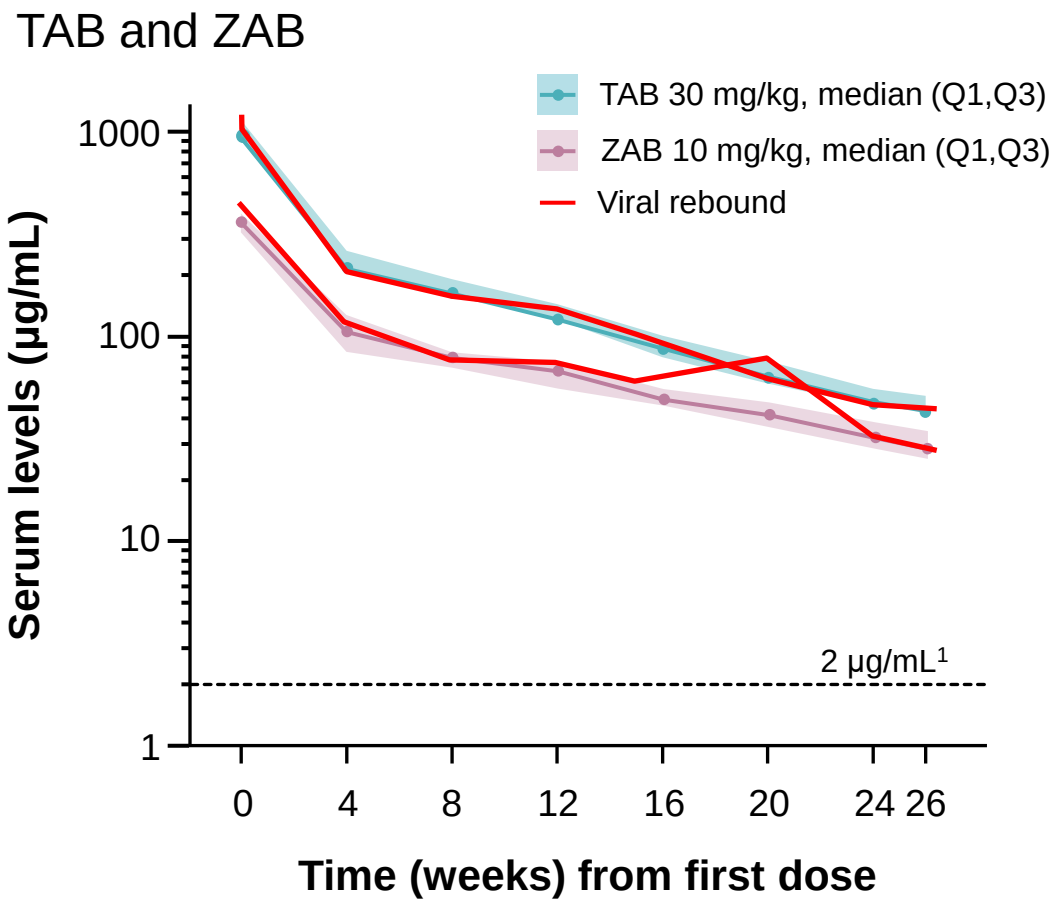
HIV-1 RNA by Study Week in Participant with Viral Rebound

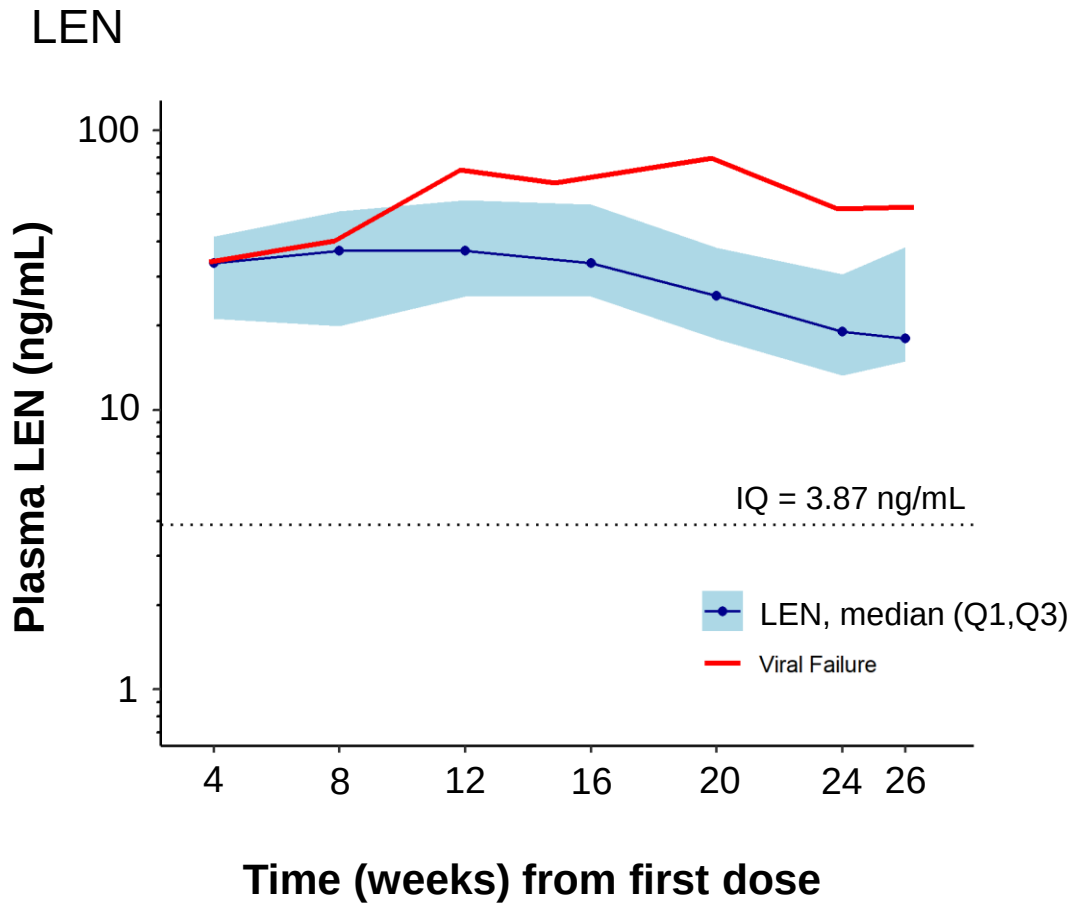


- Participant who experienced viral rebound had baseline phenotypic susceptibility to teropavimab and zinlirvimab, and no pre-existing LEN resistance mutations were detected.
  - Resistance testing of rebound samples resulted in assay failure.
- Participant's CD4 count remained above 500 through Week 26.

The limit of quantification (LOQ) is 20 copies/mL. For the rebound participant, except for Weeks 16 and 18, HIV-1 RNA levels were < 20 copies/mL.

Pharmacokinetics in Participant with Viral Rebound





- TAB, ZAB, and LEN PK for the participant who experienced viral rebound was consistent with others in their dosing group.

[1] 2 µg/mL was the level required for sensitivity in the screening assay.

Summary

- **This phase 1b study demonstrates early evidence that a combination of the bNAbs teropavimab and zinlirvimab together with lenacapavir can sustain viral suppression for 6 months in selected people with HIV.**
- 18 out of 20 participants maintained suppression for 26 weeks after a single administration of the study regimen.
  - *One withdrew after Week 12 with suppressed HIV RNA.*
  - *One had viral rebound at Week 16 and resuppressed after restarting his baseline ART.*
- LEN + TAB + ZAB was generally well tolerated, mild (Grade 1) injection-site reactions were the most common adverse event.
- LEN + TAB + ZAB may enable a complete twice-yearly HIV treatment regimen.
  - Phase 2 study (NCT05729568)

Eron J et al. CROI 2023, Oral #193; Eron J et al. BHIVA Spring Conference 2023, Oral #16.