Efficacy and Safety Analysis of Lenacapavir With Broadly Neutralising Antibodies, Teropavimab and Zinlirvimab, in People With HIV-1 Highly Sensitive to One or Both Broadly Neutralising Antibodies

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HIV Drug Therapy Glasgow, November 10–13 2024, Glasgow, UK

Disclosures

Susan J Little reports grants/contract payments made to their institution from Gilead Sciences, Inc.

Paul P Cook reports grants/contract payments from Gilead Sciences, Inc., Janssen Pharmaceuticals, Lilly, Merck, National Institutes of Health, Seres Therapeutics, and ViiV Healthcare; and data safety monitoring or advisory board participation from Westat.

Edwin DeJesus reports grants/contract payments from AbbVie, Gilead Sciences, Inc., Merck, TeroTechnology/Taimed Biologic, and ViiV Healthcare.

Gordon E Crofoot reports grants/contract payments from AbbVie, Gilead Sciences, Inc., Janssen Pharmaceuticals, Merck, and ViiV Healthcare; and support for attending meetings from Gilead Sciences, Inc.

Linda Gorgos reports grants/contract payments made to their institution from Gilead Sciences, Inc., GSK, Merck, and ViiV Healthcare; and honoraria from the AIDS Education and Training Center – South Central.

Joseph J Eron reports grants/contract payments made to their institution from Gilead Sciences, Inc. and ViiV Healthcare; and consulting fees from Abbvie, Gilead Sciences, Inc., Merck, and ViiV Healthcare.

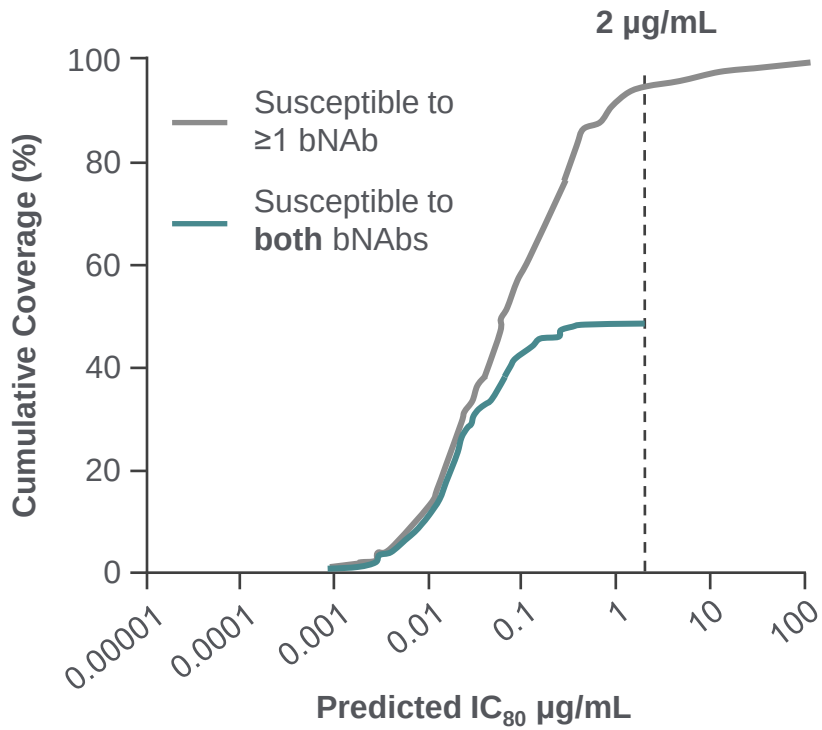
Kwad Mponponsuo, Hailin Huang, and **Sean E Collins** are all employees and shareholders of Gilead Sciences, Inc.

This study was funded by Gilead Sciences, Inc.

Background

- Teropavimab (TAB) and zinlirvimab (ZAB) are broadly neutralising antibodies (bNAbs)[1]
  - TAB targets the CD4-binding site of gp120 and ZAB targets a non-overlapping epitope on the V3 glycan of HIV-1 Env[1]
- ~50% of clade B viruses are highly susceptible to both TAB and ZAB with a 90% inhibitory concentration (IC_{90}) ≤2 µg/mL[2]
  - >90% are highly susceptible to either TAB or ZAB[2]
  - The optimal bNAb sensitivity threshold has not yet been established
- TAB and ZAB have extended half-lives that allow for dosing every 6 months[1]

TAB and ZAB Susceptibility Breadth[a]



- Lenacapavir (LEN), the first-in-class capsid inhibitor, can be administered subcutaneously (SC) every 6 months and is approved for the treatment of multidrug-resistant HIV-1[3]

[a]Estimated coverage given predicted IC_{90} closely resembles coverage given IC_{80} shown here. Data from CATNAP CombiNAber using 479 clade B viruses.[4,5]

1. Gautam R, et al. *Nat Med.* 2018; 24:610–6. 2. Selzer L, et al. CROI 2023; Poster 580. 3. Sunlenca® Summary of Product Characteristics, available at www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf (accessed October 2024). 4. Yoon H, et al. *Nucleic Acid Res*. 2015;43:W213-9. 5. Wagh K, et al. *PLoS Pathog*. 2016;12:e1005520

Objective

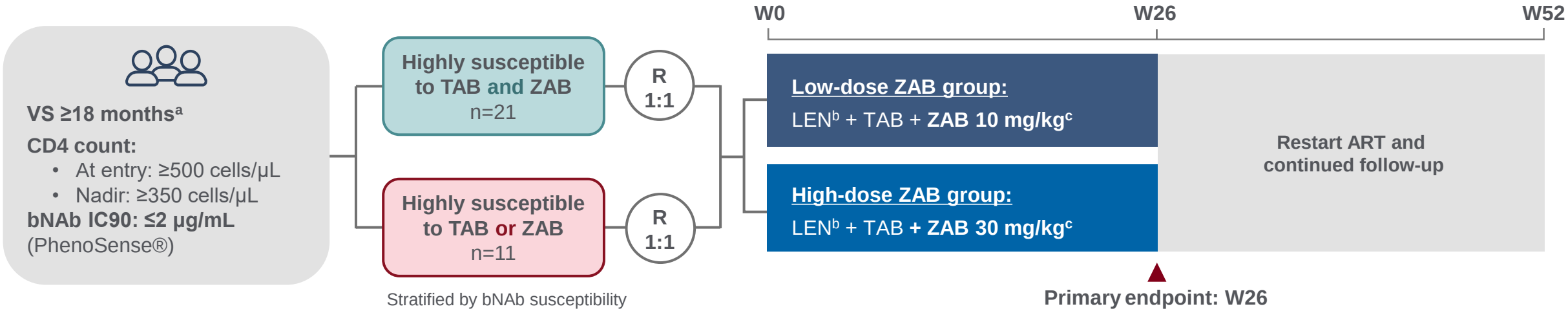
— We conducted a randomised Phase 1b study (NCT04811040)[1,2] to assess the safety and efficacy of a single dose of LEN + TAB + ZAB in virologically suppressed people with HIV-1 (PWH) who were:

- Highly susceptible to both bNAbs (primary cohort[1])
- Highly susceptible to one of TAB or ZAB (pilot cohort[2])

Here, we report pooled outcomes for both cohorts through Week 26, stratified by dose of ZAB

1. Eron J, et al. *Lancet HIV*. 2024;11:E146–55. 2. Eron J, et al. CROI 2024; Abstract 120.
bNAb, broadly neutralising antibody; **LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Study Design

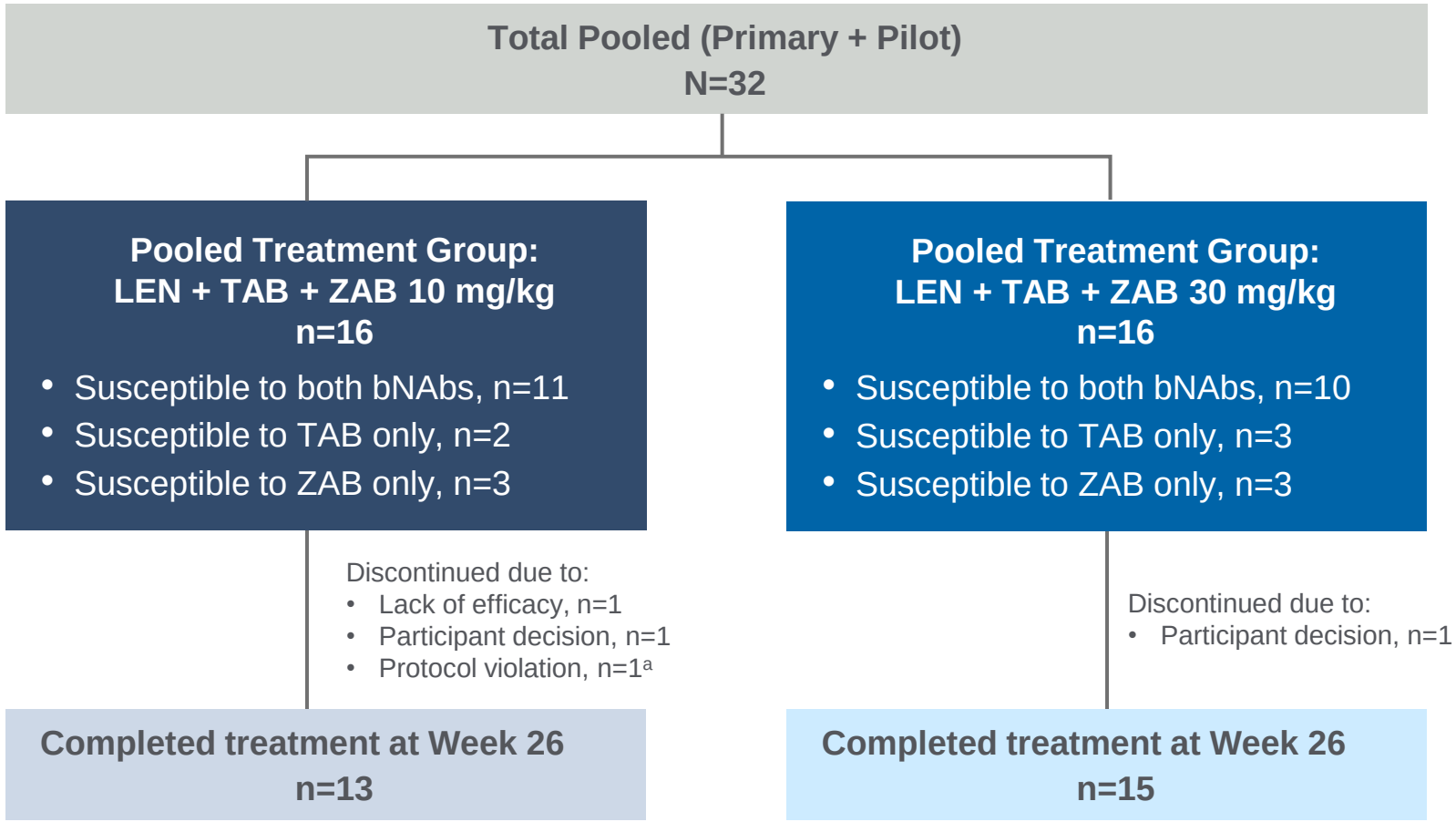


Week 26 pooled analysis outcomes:

- Efficacy at Week 26 by FDA Snapshot Algorithm
- Adverse events and laboratory abnormalities
- Anti-drug antibodies (ADAs)
- Pharmacokinetics of LEN, TAB, and ZAB

[a]Previous virologic failure was allowed if participants had VS (HIV-1 RNA ≤50 copies/mL) for ≥18 months prior to screening. [b]LEN 927 mg SC on Day 1, plus oral LEN 600 mg on Days 1 and 2. [c]TAB 30 mg/kg IV and ZAB 10 or 30 mg/kg IV on Day 1. **ART,** antiretroviral therapy; **bNAb,** broadly neutralising antibody; **IC_{90},** 90% inhibitory concentration; **IV,** intravenous; **LEN,** lenacapavir; **R,** randomised; **SC,** subcutaneous; **TAB,** teropavimab; **VS,** virologic suppression; **W,** Week; **ZAB,** zinlirvimab.

bNAb Susceptibility and Participant Disposition



[a]Due to chronic hepatitis B virus infection; participant restarted antiretroviral therapy.
bNAb, broadly neutralising antibody; **LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Baseline Characteristics

	LEN + TAB + ZAB 10 mg/kg (n=16)	LEN + TAB + ZAB 30 mg/kg (n=16)
Median (range) age, years	48 (28–63)	44 (25–59)
Female sex at birth, n (%)	2 (13)	4 (25.0)
Race, n (%)		
Asian	2 (13)	1 (6)
Black	3 (19)	4 (25)
White	10 (63)	8 (50)
Other	1 (6)	3 (19)
Hispanic or Latinx ethnicity, n (%)	6 (38)	4 (25)
Median (range) weight, kg	88 (59–150)	89 (60–143)
Median (range) CD4 cell count, cells/mL	821 (449–1916)	985 (667–1644)

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

Efficacy at Week 26

Virologic Outcomes at Week 26 by FDA Snapshot Algorithm

	LEN + TAB + ZAB 10 mg/kg (n=14[a])	LEN + TAB + ZAB 30 mg/kg (n=16)
HIV-1 RNA ≥50 copies/mL, n	**3**	**0**
HIV-1 RNA <50 copies/mL, n	**11**	**15**
No virologic data in Week 26 window, n	**0**	**1**[b]

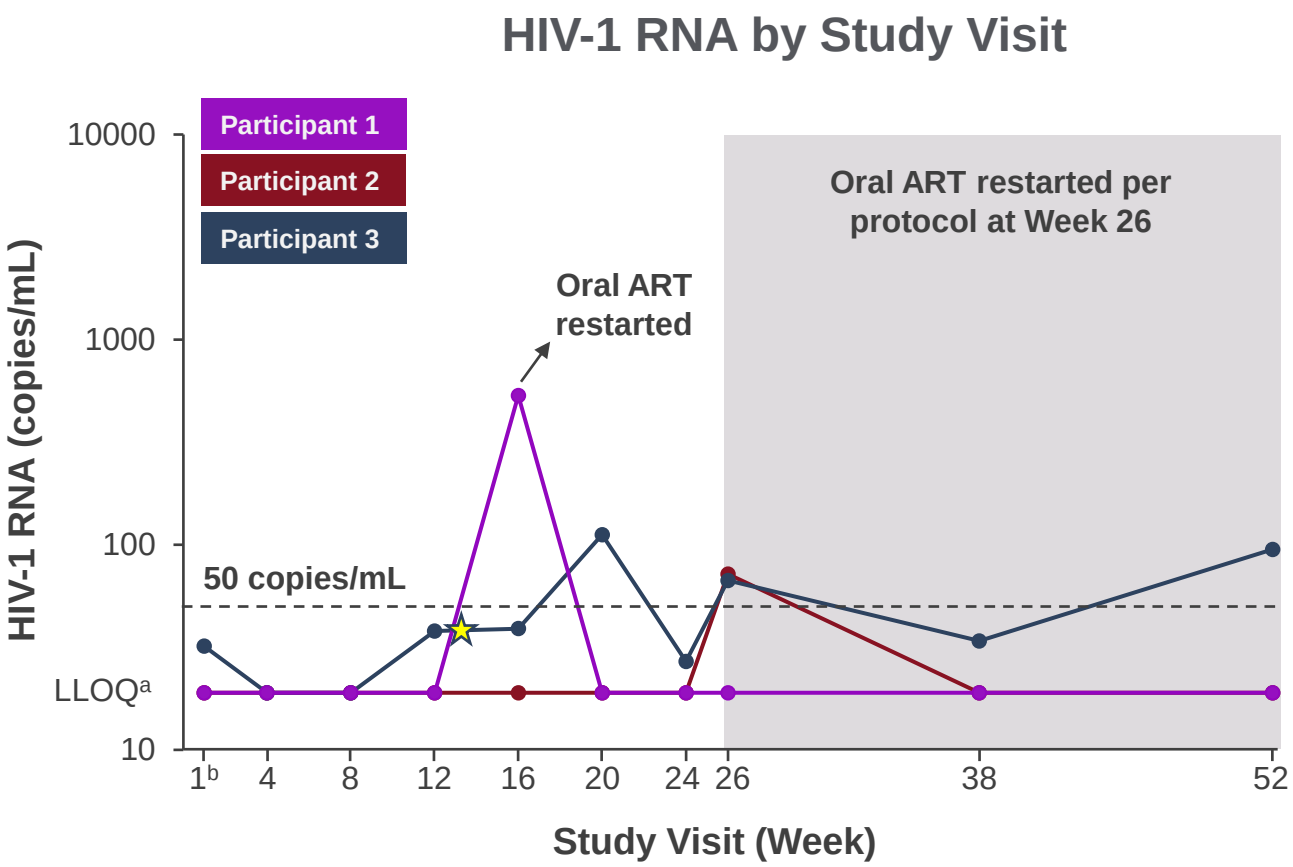
— No participants in the high-dose ZAB group had virologic rebound (HIV-1 RNA ≥50 copies/mL) 6 months after dosing

— CD4 cell counts remained stable; mean (SD) change from baseline to Week 26:

- LEN + TAB + ZAB 10 mg/kg: +5 (267) cells/mL
- LEN + TAB + ZAB 30 mg/kg: –30 (293) cells/mL

[a]Two participants were excluded from the efficacy analysis (did not receive the complete study regimen [participant decision], n=1, protocol violation, n=1). [b]Participant withdrew from the study after Week 12 (participant decision), with HIV-1 RNA <50 copies/mL at last available visit.
LEN, lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Participants with Virologic Rebound (HIV-1 RNA ≥50 copies/mL)



	Participant 1	Participant 2	Participant 3
Study group	ZAB 10 mg/kg	ZAB 10 mg/kg	ZAB 10 mg/kg
bNAb susceptibility at screening	TAB and ZAB	ZAB only	TAB only
Pre-existing LEN RAMs at screening	None	None	None
Treatment-emergent drug resistance	Q67H in CA[c]	None detected	None detected

☆ **Participant 3** had acute COVID-19 infection at Week 13, prior to viral rebound

— Only one participant with virologic rebound had documented resistance emergence (to LEN)

[a]For illustrative purposes, viral loads <20 copies/mL (the LLOQ) are shown as 19 copies/mL. [b]Day 1. [c]Commercial resistance testing methods resulted in assay failure due to low plasma viral load; resistance was evaluated using novel techniques (Selzer L, et al. AIDS 2024; Poster WEPEB146).
ART, antiretroviral therapy; **CA,** capsid; **LEN,** lenacapavir; **LLOQ,** lower limit of quantification; **RAM,** resistance-associated mutation; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Safety Overview and ADAs

n (%)	LEN + TAB + ZAB 10 mg/kg (n=15[a])	LEN + TAB + ZAB 30 mg/kg (n=16)
Treatment-emergent adverse events (TEAEs)	12 (80)	15 (94)
Grade ≥3	0	2 (13)
Treatment-related TEAEs	10 (67)	12 (75)
Grade ≥3	0	2 (13)[b]
Serious TEAEs	0	0
TEAEs leading to study drug discontinuation	0	0

- One participant (low-dose ZAB group) had an infusion-related reaction (Grade 1 pyrexia) after completing administration of both bNAbs, which resolved without treatment
- Treatment-emergent ADAs against TAB occurred in 6/31 participants, and against ZAB in 6/31 participants
  - ADAs were generally low in titres and did not impact pharmacokinetics, efficacy, or safety

[a]One participant excluded from safety analyses as they did not receive complete study regimen (participant decision). [b]Erythema (n=1) and cellulitis (n=1; occurring at LEN injection site, treated with antibiotics).
ADA, anti-drug antibody; **bNAb,** broadly neutralising antibody; **LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Most Common TEAEs

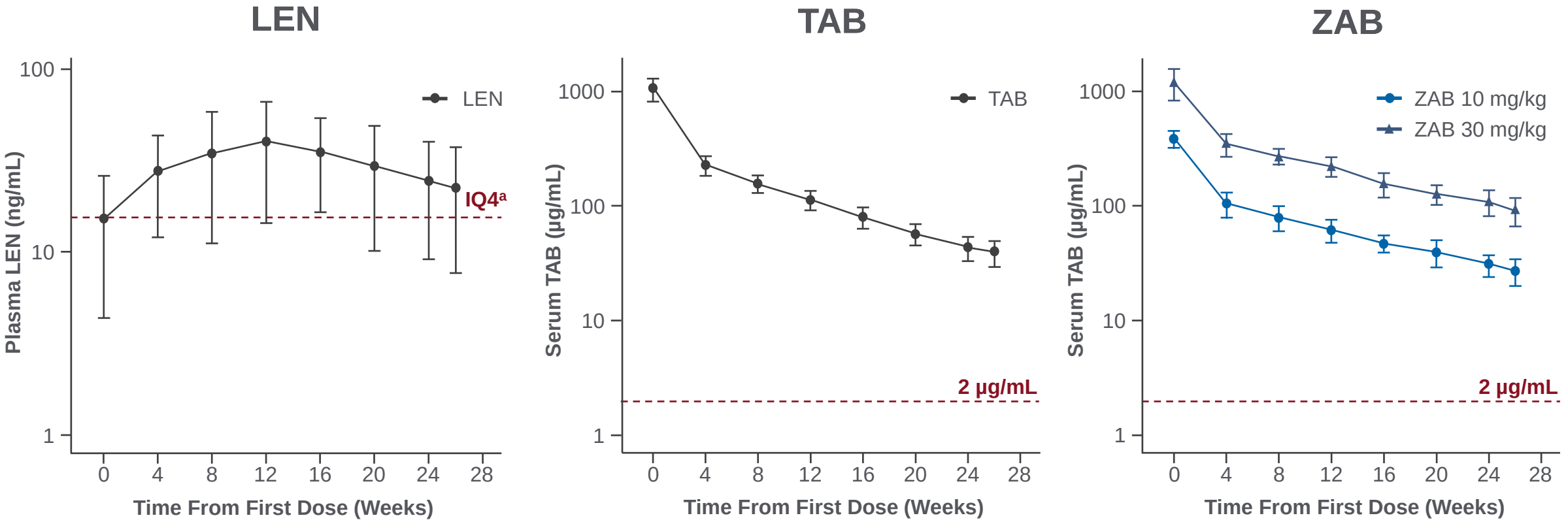
Most common TEAEs (occurring in ≥10% of participants), n (%)	LEN + TAB + ZAB 10 mg/kg (n=15[a])	LEN + TAB + ZAB 30 mg/kg (n=16)
Injection site pain	5 (33)	7 (44)
Injection site induration	2 (13)	7 (44)
Injection site erythema	4 (27)	5 (31)
Injection site nodule	5 (33)	3 (19)
COVID-19	3 (20)	1 (6)
Injection site mass	3 (20)	1 (6)
Upper respiratory tract infection	3 (20)	1 (6)

— Overall, median (IQR) durations of resolved nodules and indurations were:

- Nodules (n=8): 85 (63–194) days
- Indurations (n=8): 246 (158–305) days

[a]One participant excluded from safety analyses as they did not receive complete study regimen [participant decision].
IQR, interquartile range; **LEN,** lenacapavir; **TAB,** teropavimab; **TEAE,** treatment-emergent adverse event; **ZAB,** zinlirvimab.

Mean (SD) Drug Concentrations Over Time



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

[a]15.5 ng/mL, 4-fold higher than the *in vitro* protein-adjusted 95% effective concentration in MT 4 cells.
IQ4, inhibitory quotient 4; **LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Conclusions

- The long-acting combination of LEN + TAB + ZAB had a favourable safety profile through Week 26, with no difference in safety or tolerability between ZAB dose groups
- All participants who received LEN, TAB, and high-dose ZAB maintained viral suppression through Week 26[a]
- These results suggest high treatment efficacy for the combination of LEN, TAB, and high-dose ZAB can be achieved in PWH highly susceptible to one or both bNAbs
  - The higher ZAB dose was selected for an ongoing Phase 2 study (NCT05729568) investigating the efficacy and safety of switching to twice-yearly LEN + TAB + ZAB vs continuing baseline therapy in PWH highly susceptible to both bNAbs

[a]No data in Week 26 window, n=1.
bNAb, broadly neutralising antibody; **LEN,** lenacapavir; **PWH,** people with HIV-1; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Acknowledgements

- We extend our thanks to the participants and their families

- We would like to thank all participating investigators: Cynthia Brinson, Paul P Cook, Gordon E Crofoot, Edwin DeJesus, Joseph J Eron, Linda Gorgos, Dushyantha Jayaweera, Susan J Little, Anthony Mills, Olayemi Osiyemi, Moti N Ramgopal, Peter J Ruane, Sarah Waldman

- All authors contributed to and approved the presentation; medical writing support was provided by Jessica Woods of Ashfield MedComms (Macclesfield, UK), an Inizio company, and was funded by Gilead Sciences, Inc.

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