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Efficacy and safety analysis of lenacapavir with broadly neutralizing antibodies, teropavimab and zinlirvimab, in people with HIV-1 highly sensitive to one or both broadly neutralizing antibodies

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Background: Lenacapavir (LEN), the first-in-class HIV-1 capsid inhibitor approved for the treatment of multidrug-resistant HIV-1 infection in adults, is being evaluated as part of a twice-yearly combination treatment regimen with broadly neutralizing antibodies (bNAbs) teropavimab (TAB, GS-5423) and zinlirvimab (ZAB, GS-2872). In a randomized, phase Ib study (NCT04811040), participants received LEN + TAB with a low or high dose of ZAB. We evaluated pooled efficacy and safety of the combination regimen, stratified by dose of ZAB.

Methods: Virologically suppressed adults (HIV-1 RNA <50 copies/ml) with HIV-1, highly susceptible to both bNAbs (primary cohort) or only one bNAb (pilot cohort) by HIV-1 proviral phenotype (PhenoSense monoclonal antibody assay IC_{90} ≤2 μg/ml) were enrolled. Cohorts were randomized 1:1 to two active treatment groups: LEN (927 mg subcutaneously after oral loading) + TAB (30 mg/kg intravenously [IV]) + ZAB (low dose, 10 mg/kg IV; or

O23: Table 1. Efficacy as determined by US FDA-defined Snapshot algorithm at W26

	LEN + TAB + ZAB 10 mg/kg (*n* = 14)	LEN + TAB + ZAB 30 mg/kg (*n* = 16)
HIV-1 RNA ≥50 copies/ml, *n* (% [95% CI])	3 (21.4 [4.7–50.8])	0 (0.0 [0.0–20.6])
HIV-1 RNA <50 copies/ml, *n* (% [95% CI])	11 (78.6 [49.2–95.3])	15 (93.8 [69.8–99.8])
No virological data in W26 window, *n* (%) (discontinued study drug due to other reasons[a] and last available HIV-1 RNA <50 copies/ml)	0	1[b] (6.3)

Abbreviations: AE, adverse event; LEN, lenacapavir; TAB, teropavimab; W, week; ZAB, zinlirvimab.
[a]Reasons other than AE/death or lack of efficacy (e.g. discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, non-compliance with study drug, protocol violation, pregnancy or study terminated by sponsor). [b]Withdrew from the study after W12.

high dose, 30 mg/kg IV). Week 26 data for the primary cohort have been previously reported [1]. In this analysis, we assessed pooled virological outcomes (using US FDA Snapshot algorithm) and safety of both cohorts by treatment group through Week 26.

Results: Thirty-two participants were randomized; 31 received the complete study regimen; one restarted antiretroviral therapy due to a major protocol violation and was excluded from analyses. Participants were: 19% female, 22% Black and 31% Hispanic/Latinx. At baseline, median age was 48 years and mean CD4 count was 992 cells/μl. At week 26, 3/14 (21%) in the low dose, and 0/16 (0%) in the high dose group had HIV-1 RNA ≥50 copies/ml (Table 1). There were no serious adverse events (AEs) related to study drug; the most common AEs were injection site reactions related to subcutaneous LEN administration.

Conclusions: All participants who received LEN, TAB and high-dose ZAB maintained viral suppression with no difference in safety or tolerability between dose groups. These early phase results suggest that high treatment efficacy for the long-acting regimen of LEN, TAB and high-dose ZAB can be achieved when at least one antibody is highly active in people with HIV highly susceptible to one or both bNAbs.

Reference

1. Eron JJ, Little SJ, Crofoot G, Cook P, Ruane PJ, Jayaweera D, et al. Safety of teropavimab and zinlirvimab with lenacapavir once every 6 months for HIV treatment: a phase 1b, randomised, proof-of-concept study. Lancet HIV. 2024;11:e146-55.