Resistance Analyses During Treatment of Lenacapavir with Broadly Neutralizing Antibodies in People with HIV

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Conclusions

- High rates of virologic suppression (n=27/30) were maintained through Week 26 of treatment with lenacapavir (LEN) plus the two broadly neutralizing antibodies (bNAbs), teropavimab (TAB) and zinlirvimab (ZAB), including among participants highly susceptible to only one bNAb
- Development of low copy number genotyping allowed genotypic and phenotypic resistance analyses in three participants with low-level (>50 to <1000 copies/mL) virologic rebound (VR)
  - Treatment-emergent LEN resistance was only detected in one of the three analyzed participants
  - None of the three participants showed treatment-emergent resistance to TAB or ZAB
- All three participants with VR received ZAB 10 mg/kg, suggesting that a higher dose of ZAB may decrease risk of VR

Plain Language Summary

- Lenacapavir is a medicine approved for the treatment of HIV in people who have received many different HIV medicines, and for whom many currently approved medicines no longer work
- Teropavimab and zinlirvimab are drugs known as antibodies that are being tested as new treatments for HIV
- Lenacapavir, teropavimab, and zinlirvimab can be given as an injection once every 6 months. The combination of these three drugs is being tested as a different way of taking HIV medicines rather than as tablets every day
- The first clinical trial looking at these three drugs together included people receiving treatment for HIV who had no detectable HIV in their blood
- After receiving the combination of lenacapavir, teropavimab, and zinlirvimab with no other HIV medicines, most people still did not have HIV found in their blood after 26 weeks (or 6 months)
- Three people had low levels of HIV in their blood while on these three drugs
- We looked to see if lenacapavir, teropavimab, or zinlirvimab stopped working in any of the patients (also called resistance)
- We found that HIV became resistant to lenacapavir in only one person, and none had HIV virus that had become resistant to teropavimab or zinlirvimab

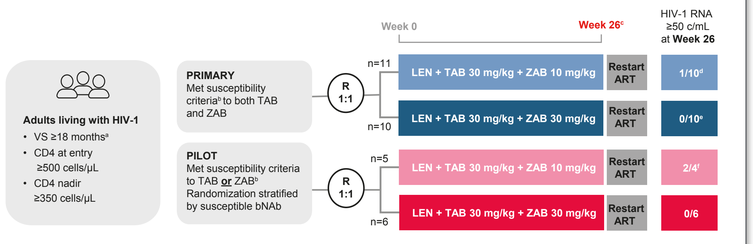
Background

- Long-acting injectable antiretroviral (ARV) treatment regimens are alternatives to daily oral regimens, and may help overcome barriers to treatment adherence
- LEN is a first-in-class, long-acting, potent HIV-1 capsid inhibitor administered by subcutaneous (SC) injection Q6M following initial oral loading[3]
  - LEN is approved in the EU, US, and other countries for the treatment of HIV-1 in people living with HIV that are heavily treatment-experienced with multidrug resistance, in combination with other ARVs[4,5]
  - LEN is being investigated for other potential uses in HIV treatment and prevention
- TAB and ZAB are bNAbs that target the CD4-binding site and a non-overlapping epitope on the V3 glycan of HIV-1 Env, respectively[1]
  - >90% of Clade B HIV viruses are highly susceptible to either TAB or ZAB, and >50% are highly susceptible to *both* TAB and ZAB (using a 90% inhibitory concentration [IC_{90}] of <2 µg/mL)[2]
  - TAB and ZAB are human antibodies that have been modified to extend their half-lives to allow for once-every-6-month (Q6M) intravenous dosing
- LEN, TAB, and ZAB are all suitable for Q6M dosing, and are being examined in combination as a long-acting treatment for people with HIV

Study Background

- In a Phase 1b study (**Figure 1**, NCT04811040), a single dose of the long-acting combination of LEN, TAB, and ZAB maintained virologic suppression (VS) for 6 months in a primary cohort of 18/20 participants with HIV-1 highly susceptible to both bNAbs, and in 8/10 participants in a pilot cohort who were highly susceptible to *either* TAB or ZAB[6,7]

Figure 1. Study Design



[a]Previous virologic failure was allowed if participants were VS (HIV-1 RNA <50 copies/mL) for ≥18 months prior to screening; [b]bNAb susceptibility defined as an IC_{90} ≤2 µg/mL by PhenoSense mAb Assay (Monogram Biosciences). [c]At Week 26, all participants restarted their previous ART regimen and follow-up continued to Week 52. [d]One participant withdrew prior to receiving study drug and is excluded from the efficacy analysis. [e]One participant withdrew for reasons other than AE/death or lack of efficacy at Week 12, with last on study HIV-1 RNA <50 c/mL before restarting oral ART. [f]One participant restarted ART prior to Week 26 due to a protocol violation (chronic HBV) and is excluded from the efficacy analysis.
AE, adverse event; ART, antiretroviral therapy; bNAB, broadly neutralizing antibodies; HBV, hepatitis B virus; IC_{90}, 90% inhibitory concentration; mAb, monoclonal antibody; R, randomization; TAB, teropavimab; VS, virologic suppression; ZAB, zinlirvimab.

Objective

- To investigate treatment-emergent resistance through Week 26 in participants treated with LEN + TAB + ZAB in a Phase 1b study

Methods

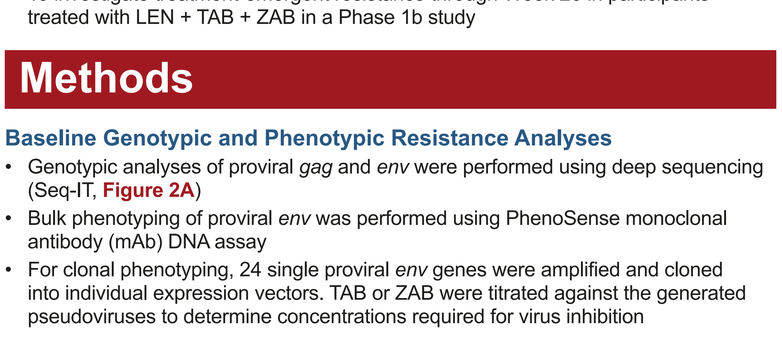
Baseline Genotypic and Phenotypic Resistance Analyses

- Genotypic analyses of proviral *gag* and *env* were performed using deep sequencing (Seq-IT, **Figure 2A**)
- Bulk phenotyping of proviral *env* was performed using PhenoSense monoclonal antibody (mAb) DNA assay
- For clonal phenotyping, 24 single proviral *env* genes were amplified and cloned into individual expression vectors. TAB or ZAB were titrated against the generated pseudoviruses to determine concentrations required for virus inhibition

Post-Baseline Genotypic and Phenotypic Resistance Analyses

- Per-protocol resistance analyses were performed at Virologic Failure (VF; HIV-1 RNA ≥200 copies/mL on two consecutive visits or at study discontinuation/Week 26)
- Exploratory analyses were performed at VR (HIV-1 RNA ≥50 copies/mL on two consecutive visits or at study discontinuation/Week 26)
  - Commercial genotyping and phenotyping methods were unsuccessful, likely due to low virus copy numbers (**Figure 2B**)
  - A novel assay amenable to low virus copy number samples was performed by selecting primers to amplify and sequence capsid and a 1 kb stretch of *gp120* (nt# 102–1092) from rebound viruses (**Figure 2C**)
- To determine phenotypic susceptibility to LEN, TAB, and ZAB, the capsid gene and the 1kb stretch of *gp120* sequenced from rebound viruses were synthesized and cloned into majority sequences for *gag* and *env* determined at baseline. Chimeric *gag* and *env* genes were phenotyped using PhenoSense Gag-Pro and mAb assays, respectively (**Figure 2C**)
- Viral susceptibility to bNAbs was defined as having an IC_{90} of ≤2 µg/mL[6]

Figure 2. Resistance Analyses



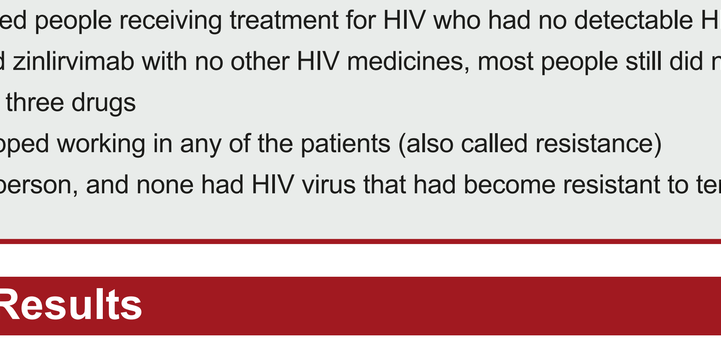
mAb, monoclonal antibody.

Results

Study Population

- Baseline TAB and ZAB HIV-susceptibility data from all participants in the Phase 1b study are shown in **Figure 3**
- Three participants in the Phase 1b study met criteria for VR and were included in the resistance analyses
  - One participant from the primary cohort, 10 mg/kg ZAB group
  - Two participants from the pilot cohort, 10 mg/kg ZAB group

Figure 3. Baseline TAB and ZAB Susceptibility



IC_{90}, 90% inhibitory concentration; TAB, teropavimab; ZAB, zinlirvimab.

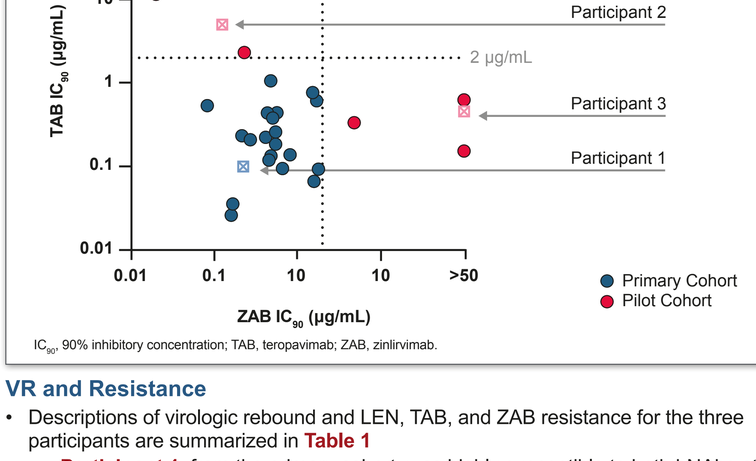
VR and Resistance

- Descriptions of virologic rebound and LEN, TAB, and ZAB resistance for the three participants are summarized in **Table 1**
  - **Participant 1**, from the primary cohort, was highly susceptible to both bNAbs at baseline and showed VR at Week 16, with resistance to LEN detected, but not to TAB or ZAB (**Figure 4A**)
  - **Participant 2**, from the pilot cohort, was highly susceptible only to ZAB at baseline and showed VR at Week 26, with no treatment emergent resistance detected (**Figure 4B**)
  - **Participant 3**, from the pilot cohort, was highly susceptible only to TAB at baseline and showed VR at Week 26, with no treatment emergent resistance detected (**Figure 4C**)

Clonal Analysis

- To further investigate susceptibility to TAB and ZAB at baseline in participant with emergent LEN resistance (Participant 1), baseline clonal phenotypic analysis of Env was performed (**Figure 5A**)
- Baseline phenotypic resistance to either TAB or ZAB was not detected (**Figure 5B,C**)
  - Of the 24 screened clones, 23/24 clones had an IC_{90} ≤2 µg/mL for TAB and all clones had an IC_{90} ≤2 µg/mL for ZAB

Figure 5. Baseline Clonal Analysis



C

	TAB (µg/mL)	ZAB (µg/mL)
Original bulk screening IC_{90}	0.222	0.263
Clonal analysis geometric mean IC_{90} (range)	0.355 (0.203–3.960)	0.134 (0.064–0.288)

Dotted line in Figure 5B represents the 2 µg/mL IC_{90} cutoff.
IC_{90}, 90% inhibitory concentration, TAB, teropavimab; ZAB, zinlirvimab.

Figure 4A. Viral Response and Resistance – Participant 1

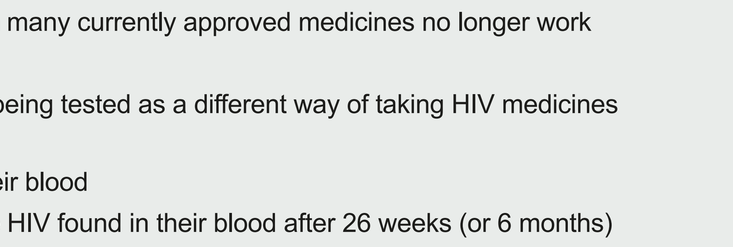
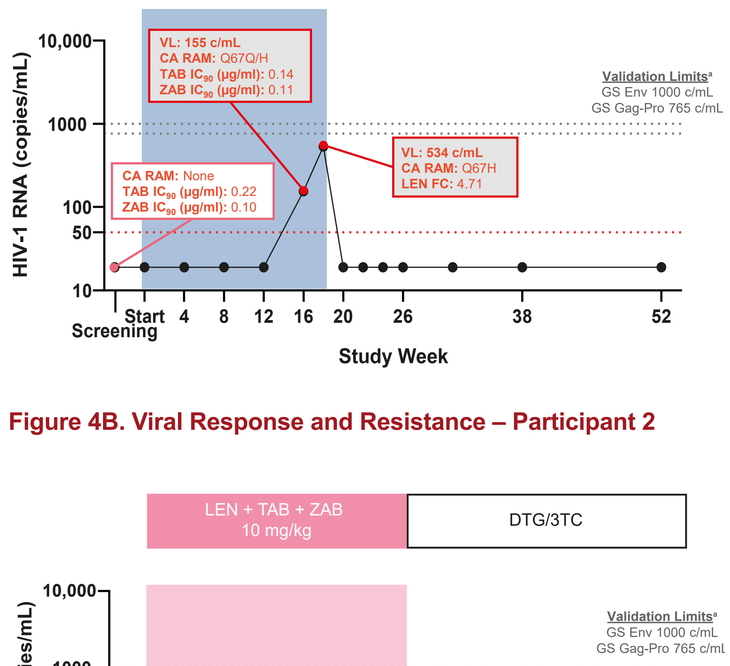


Figure 4B. Viral Response and Resistance – Participant 2

Figure 4C. Viral Response and Resistance – Participant 3



Red dotted line denotes the 50 copies/mL limit which defined virologic rebound in this study.
[a]Validation limits for the GenoSure® *Env* and the GeneSeq® *Gag* assays.
ART, anti retroviral treatment; bNAbs, broadly neutralizing antibodies; CA, capsid; DTG/3TC, Dolutegravir/lamivudine; FC, fold change; IC_{90}, 90% inhibitory concentration, LEN, lenacapavir; RAM, resistance associated mutation; RPV/F/TAF, rilpivirine, emtricitabine, and tenofovir alafenamide; TAB, teropavimab; VL, viral load; VR, virologic rebound; W, week; ZAB, zinlirvimab.

Table 1. Resistance Summary

Baseline						Post-Baseline					
Participant	Cohort	Sub-type	Treatment group	Baseline IC_{90} (µg/ml)		Virologic rebound visit	HIV-1 RNA at virologic rebound visit (copies/mL)	Emerging LEN RAMs	In-vitro FC (Gag-Pro)[a,b]	In-vitro FC from baseline (PhenoSense mAb)[a]	
				TAB	ZAB				LEN	TAB	ZAB
1	Primary	B	LEN + TAB + ZAB 10 mg/kg	0.22	0.10	Week 16 Week 16-Retest	155 534	Q67Q/H Q67H	ND 4.71	0.66 ND[c]	1.18 ND[c]
2	Pilot	B	LEN + TAB + ZAB 10 mg/kg	5.02*	0.12	Week 26	72	none	AF	1.02	1.09
3	Pilot	B	LEN + TAB+ ZAB 10 mg/kg	0.43	>50[†]	Week 26	55	none	0.52	0.30	1.00

*note: reduced susceptibility to TAB; †note: full resistance to ZAB.
[a]Phenotyping of *gag* and *env* was performed at VR based on the majority sequence determined from genotyping. [b]Fold-change relative to wild-type HIV-1 strain NL4.3.[c]PhenoSense mAb could not be determined due to assay failure during genotyping.
AF, assay failure; FC, fold change, IC_{90}, 90% inhibitory concentration, LEN, lenacapavir; mAb, monoclonal antibody; ND, not determined; PR, protease; RAM, resistance associated mutation; RT, reverse transcriptase; TAB, teropavimab; VR, viral rebound; ZAB, zinlirvimab.

References: **1**. Gautam R, et al. *Nat Med* 2018; 24(5): 610–6. **2**. Selzer L, et al. Presented at CROI 2023. Poster 580. **3**. Link JO, et al. *Nature*. 2020;584:614–8. **4**. Sunlenca® Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf (Accessed May 2024). **5**. Sunlenca® Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-productinformation_en.pdf (Accessed May 2024). **6**. Eron J, et al. *Lancet HIV.* 2024 Mar;11(3):e146–e155. **7**. Eron J, et al. Presented at CROI 2024. Presentation #2258.

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