Phase 2 Pharmacokinetics and Anti-Drug Antibody Results of the Investigational Twice-Yearly HIV-1 Treatment Regimen Lenacapavir, Teropavimab, and Zinlirvimab

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Conclusions

- Lenacapavir (LEN), teropavimab (TAB), and zinlirvimab (ZAB) have prolonged half-lives, supporting twice-yearly dosing in virologically suppressed (VS) people with HIV-1 (PWH)
- Mean therapeutic concentrations of LEN, TAB, and ZAB were maintained at Week 52, with minimal drug accumulation over time
- There was a low incidence of anti-drug antibodies (ADA)/neutralizing antibodies (NAb) against TAB and ZAB, and ADA titers were generally low
- No association was observed between ADAs/NAbs and pharmacokinetics (PK)

Plain Language Summary

- HIV attacks cells that help our bodies fight infections. Having HIV that is not treated makes people more likely to get other infections
- Lenacapavir is a medicine that is approved to treat HIV in people who have tried many different HIV medicines. Lenacapavir is given as injections
- Teropavimab and zinlirvimab are new medicines given as an infusion (into a vein) that are being tested to treat HIV
- Lenacapavir, teropavimab, and zinlirvimab can be given together once every 6 months. This is different from most HIV treatments that involve taking pills every day
- These three medicines are being tested together in a study. People who took part in this study were taking daily oral pills and had very low levels of HIV virus in their blood (called virologic suppression)
  - Most participants in this study still had very low levels of HIV 6 months after switching to treatment with lenacapavir, teropavimab, and zinlirvimab
- We also looked at the amount of these medicines that stayed in the blood over time. We found that the levels of all three medicines stayed high enough to work for 6 months after a single dose
- Only a small number of participants developed antibodies (a type of protein made by the immune system) against teropavimab and zinlirvimab, and the levels of these antibodies were low
  - These antibodies did not affect how teropavimab and zinlirvimab were processed by the body

Background

- TAB and ZAB are broadly neutralizing antibodies (bNAbs) under investigation as a complete twice-yearly combination-treatment regimen with LEN
- An ongoing Phase 2 study (NCT05729568) reported efficacy and safety of twice-yearly LEN, TAB, and ZAB in VS PWH consistent with daily oral antiretroviral therapy (ART)[1]
- In the ongoing Phase 2 study, PK of LEN, TAB, and ZAB, as well as the immunogenicity against TAB and ZAB, were monitored to support the evaluation of dosing and safety, and to inform efficacy following twice-yearly dosing in the VS population
  - PK and ADA samples were collected at multiple timepoints through Week 52

Objective

- To assess PK, ADA and NAb through Week 52 of treatment with LEN, TAB and ZAB

Methods

- Virologically suppressed PWH on oral ART were screened, and those who met study entry criteria were randomized to receive LEN, TAB and ZAB or continue oral ART as previously described[1] (**Figure 1**)
- TAB and ZAB were administered as 30-minute sequential intravenous (IV) infusions at 2550 mg each on Day 1 and Week 26
- Plasma samples of LEN were tested with a validated liquid chromatography-mass spectrometry method
- Non-compartmental analyses based on LEN, TAB, and ZAB concentration data were conducted with WinNonLin© software

bNAb Drug Concentration Measurements

- Serum concentrations of TAB and ZAB were quantified using fully validated electrochemiluminescence (ECL) immunoassays. These assays employed anti-idiotypic antibodies for both capture and detection (**Figure 2A**). The validated quantitative ranges were 100–10,000 ng/mL for TAB and 100–6,000 ng/mL for ZAB (**Figure 2A**)

bNAb Immunogenicity Assessments

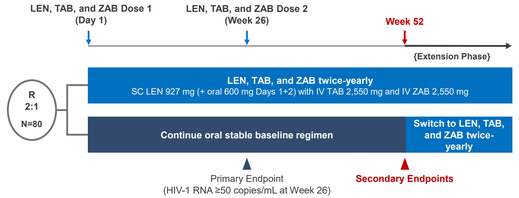
The presence of anti-TAB and anti-ZAB ADAs in human serum samples was assessed using fully validated ECL immunoassays. In this assay, biotin-drug was used as the capture reagent, and sulfo-tag-labelled drug served as the detection reagent (**Figure 2B**). A standard three-tiered bridging ADA assay approach was employed:

1. Screening assay – a highly sensitive assay to detect potential ADA presence
2. Confirmatory assay – samples detected positive in the screening assay were further tested to verify the specificity of the detected antibodies to the therapeutic drug
3. Titer assay – provided a semi-quantitative measure of ADA levels in samples that tested positive in the confirmatory assay

- Samples that tested positive for ADA were further characterized for neutralization activity against TAB or ZAB using a validated competitive ligand binding assay. In this assay, target gp120 was used as the capture reagent, and sulfo-TAG-labelled drug served as the detection reagent (**Figure 2C**)

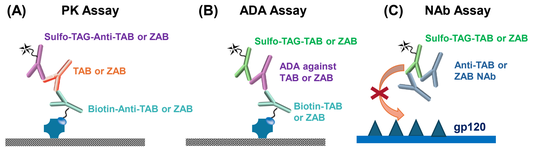
Methods (continued)

Figure 1: Phase 2 Study Design



IV, intravenous; LEN, lenacapavir; R, randomized; SC, subcutaneous; TAB, teropavimab; ZAB, zinlirvimab.

Figure 2. Bioanalytical Methods for TAB and ZAB



A) PK assay determines the TAB and ZAB concentrations. B) ADA assay (1) detects, (2) confirms and (3) determines the titer of ADAs against TAB or ZAB at each timepoint. C) NAb assay is performed in participants who are ADA positive to detect the potential interference of ADA with bNAb binding to gp120.
ADA, anti-drug antibody; MSD, Meso Scale Discovery; NAb, neutralizing antibody; PK, pharmacokinetics; TAB, teropavimab; ZAB, zinlirvimab.

Results

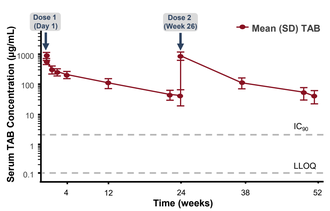
- Fifty-three participants received LEN, TAB, and ZAB

Pharmacokinetics

- Following IV administration of TAB and ZAB, both at 2,550 mg, bNAb serum concentrations reached maximum concentration (C_{max}) immediately after dosing and then decreased over time (**Figure 3** and **Figure 4**)
- Half-lives of TAB and ZAB were 63.5 and 89.1 days, respectively (**Table 1**)
- The mean trough concentration (C_{trough}) (% coefficient of variation) of TAB and ZAB were 41.8 (54.2%) and 72.0 (54.5%) µg/mL at Week 26, and 43.1 (39.5%) and 56.6 (47.3%) µg/mL at Week 52, respectively, which are more than 20x higher than the 90% inhibitory concentration (IC_{90}) cutoff of baseline viral sensitivity to TAB and ZAB in this study
- Limited accumulation was observed after the second dose of TAB and ZAB
- After the Day 1 subcutaneous (SC) LEN dose (plus oral loading on Day 1+2), mean (90% confidence interval [CI]) C_{trough} was 20.2 ng/mL (17.8; 22.7) at Week 26 (n=52); after the second SC LEN dose at Week 26, mean (90% CI) C_{trough} was 25.8 ng/mL (22.3; 29.3) at Week 52 (n=46) (**Figure 5** and **Table 2**)
- Mean LEN concentrations were above the 4-fold inhibitory quotient (IQ4; 15.5 ng/mL) for wild-type HIV-1 at both timepoints
- LEN exposures were consistent with those observed in other HIV-1 treatment populations receiving LEN as part of their ART regimen

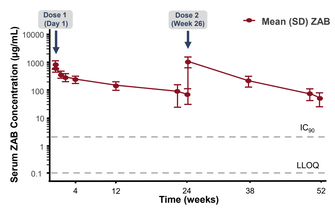
Results (continued)

Figure 3. Mean PK Profiles of TAB Dosing



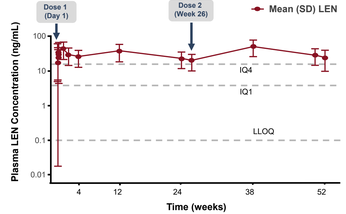
Reference lines indicate IC_{90} and LLOQ. IC_{90} was defined as 2 µg/mL for TAB; LLOQ was defined as 0.1 ug/mL for TAB.
IC_{90}, 90% inhibitory concentration; LLOQ, lower limit of quantification; PK, pharmacokinetic; SD, standard deviation; TAB, tenopavimab

Figure 4. Mean PK Profiles of ZAB Dosing



Reference lines indicate IC_{90} and LLOQ. IC_{90} was defined as 2 µg/mL for ZAB; LLOQ was defined as 0.1 ug/mL for ZAB.
IC_{90}, 90% inhibitory concentration; LLOQ, lower limit of quantification; PK, pharmacokinetic; SD, standard deviation; ZAB, zinlirvimab.

Figure 5. Mean PK Profiles of LEN Dosing



Reference lines indicate LLOQ (0.1 ng/mL), IQ1 (3.87 ng/mL), and IQ4 (15.5 ng/mL).
IQ1, inhibitory quotient 1; IQ4, inhibitory quotient 4; LEN, lenacapavir; LLOQ, lower limit of quantification; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation.

Table 1. Statistical Summary of Non-Compartmental PK Parameters of TAB and ZAB

	TAB (N=53)		ZAB (N=53)	
	Dose on Day 1 (n=53)	Dose at Week 26 (n=49)[b]	Dose on Day 1 (n=53)	Dose at Week 26 (n=49)[b]
Mean (CV%) C_{trough} (µg/mL)	41.8 (54.2)[a]	43.1 (39.5)[b]	72.0 (54.5)[a]	56.6 (47.3)[b]
Mean (CV%) $t_{1/2}$ (days)	63.5 (20.1)	NC	89.1 (45.8)[c]	NC
Mean (CV%) C_{max} (µg/mL)	918 (29.3)[a]	919 (28.7)	893 (31.1)[a]	1,100 (41.4)
Median (range) T_{max} (hour)	1.58 (1.28, 23.0)[a]	1.63 (0.900, 2.22)	0.718 (0.466, 23.3)[a]	0.701 (0.499, 1.82)
Mean (CV%) AUC_{tau} (day•µg/mL)	26,900 (29.7)	40,100 (29.8)[c]	34,400 (32.0)[c]	56,100 (24.5)[c]

[a]One participant had early study drug discontinuation without PK collection at Week 26 pre-dose (n=52). [b]Three participants had early study drug discontinuation without PK collection of LEN, TAB and ZAB at Week 52 predose (n=49) and another three participants had missing Week 52 predose concentration of LEN (n=48). [c]TAB half-lives are not calculable for three participants (n=46); ZAB half-lives are not calculable for one and nine participants after the dose on Day 1 (n=52) and Week 26 (n=40), respectively. [d]Two participants had unexpected low end of infusion concentration (n=51).
AUC_{tau}, area under the curve over the dosing interval; C_{max}, maximum concentration; C_{trough}, trough concentration; CV, coefficient of variation; LEN, lenacapavir; NC, not calculated (due to sparse sampling); PK, pharmacokinetic; $t_{1/2}$, half-life; TAB, teropavimab; T_{max}, time to maximum drug concentration; ZAB, zinlirvimab.

Table 2. Statistical Summary of Non-Compartmental PK Parameters of LEN

	LEN	
	Dose on Day 1 (n=53)	Dose at Week 26 (n=49)[b]
Mean (90% CI) C_{trough} (ng/mL)	20.2 (17.8, 22.7)[a]	25.8 (22.3, 29.3)[b]
Mean (CV%) C_{trough} Day 1 (ng/mL)	34.2 (87.7)[c]	NC
Median (range) T_{max} Day 1 (hour)	4.03 (2.15, 24.0)[c]	NC
Mean (CV%) C_{max} (ng/mL)	58.7 (58.2)[d,e]	NC
Median (range) T_{max} (hour) [days]	170 (2.16, 4,370) [7.08][d,e]	NC

[a]One participant had early study drug discontinuation without PK collection at Week 26 pre-dose (n=52). [b]Three participants had early study drug discontinuation without PK collection of LEN, TAB, and ZAB at Week 52 predose (n=49) and another three participants had missing Week 52 predose concentration of LEN (n=46). [c]C_{max}, Day 1, T_{max}, Day 1: C_{max} and T_{max} were only calculated for PK substudy participants (n=31).[d]Time when maximum exposure was reached after one or two oral doses and one SC dose. [e]Two participants had unexpected low end of infusion concentration (n=51).
CI, confidence interval; C_{max}, maximum concentration; C_{trough}, trough concentration; CV, coefficient of variation; LEN, lenacapavir; NC, not calculated (due to sparse sampling); PK, pharmacokinetic; SC, subcutaneous; T_{max}, time to maximum concentration.

Table 3. Summary of Overall Immunogenicity Results

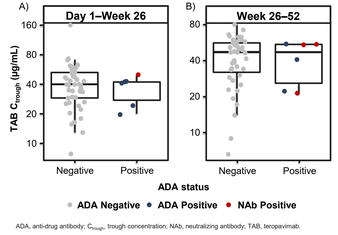
	Anti-TAB total (n=53)	Anti-ZAB total (n=53)
Evaluable for ADA incidence (with reportable ADA result post-baseline)	53	53
ADA-negative (no treatment-emergent ADA)	47 (88.7)	44 (83.0)
Treatment-emergent ADA positive (ADA incidence)	6 (11.3)	9 (17.0)
Treatment-induced ADA	6 (11.3)	9 (17.0)
Transient positive	4 (7.5)	3 (5.7)
Persistent positive	2 (3.8)	6 (11.3)
Treatment-boosted ADA	0	0
Treatment-emergent NAb positive (NAb incidence)	3 (5.7)	3 (5.7)
Median (range) ADA onset time (days)	182 (83–183)	84 (81–183)
ADA titer range	<10–1,280	<10–160

ADA samples were collected at Day 1, Weeks 4, 12, 26, 38, and 52.
Persistent ADA, treatment-induced ADA detected at ≥2 sampling time points, where the first and last ADA-positive sample are separated by a period of ≥16 weeks, or treatment-induced ADA detected at the last sampling time point of the study; Transient ADA, treatment-induced ADA that does not meet the definition of persistent ADA; Treatment-emergent ADA, includes either treatment-boosted or treatment-induced ADAs; Treatment-induced ADA, negative or missing baseline ADA sample and ≥1 positive post-baseline ADA sample; Treatment-boosted ADA, positive baseline ADA sample ≥1 positive post-baseline ADA sample, and the ratio of the max titer of the post-baseline ADA and the titer of baseline ADA ≥4.
ADA, anti-drug antibody; NAb, neutralizing antibody; TAB, teropavimab; ZAB, zinlirvimab.

Immunogenicity

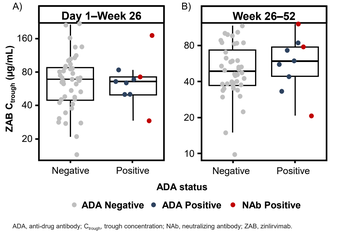
- Out of 53 participants evaluable for ADA incidence, six participants (11.3%) had treatment-emergent ADA against TAB, and nine participants (17.0%) had treatment-emergent ADA against ZAB (**Table 3**)
  - Five of these participants (9.4% of total evaluable participants) had treatment-emergent ADA against both TAB and ZAB
  - All treatment-emergent ADA were treatment induced
- Three of the six participants with ADA against TAB had treatment-emergent NAb against TAB, and three of the nine participants with ADA against ZAB had treatment-emergent NAb against ZAB (**Table 3**)
  - Two of these participants had treatment-emergent NAbs against both TAB and ZAB
- ADA titer range was generally low for both TAB and ZAB
- Median (range) ADA onset time was ~6 months for TAB and ~3 months for ZAB
- There was no impact of ADAs or NAbs on the PK of TAB (**Figure 6**) or ZAB (**Figure 7**)

Figure 6. Distribution of C_{trough} at Day 1–Week 26 (A) and Week 26–52 (B) by ADA Status of TAB



ADA, anti-drug antibody; C_{trough}, trough concentration; NAb, neutralizing antibody; TAB, teropavimab.

Figure 7. Distribution of C_{trough} at Day 1–Week 26 (A) and Week 26–52 (B) by ADA Status of ZAB



ADA, anti-drug antibody; C_{trough}, trough concentration; NAb, neutralizing antibody; ZAB, zinlirvimab.

References: 1. Ogbuagu O, et al. Presented at CROI 2025, March 9–12, San Franciso, CA, UK; Presentation 151.

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Disclosures: Nan Zhang, Jianmin Li, Hui Liu, Kwad Mponponsuo, Sean E. Collins, and **Yanan Zheng** are all employees and shareholders of Gilead Sciences, Inc.