Susceptibility Screening to bNAbs Teropavimab (GS-5423) and Zinlirvimab (GS-2872) in ART-Suppressed Participants

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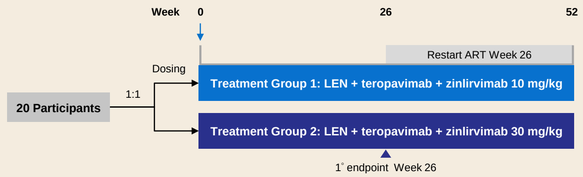
Introduction

- Broadly neutralizing antibodies (bNAbs) display strong antiviral activity by targeting the HIV-1 envelope (Env) with high potency.
- High intrapatient HIV-1 diversity within the Env gene can lead to natural resistance, posing challenges for the application of bNAbs as antiviral therapies.
- Screening patients for susceptibility to bNAbs may aid in identifying people eligible to receive bNAb therapy.
- We compared genotypic and phenotypic assays to determine participants' susceptibility to teropavimab (GS-5423; 3BNC117-LS) and zinlirvimab (GS-2872; 10-1074-LS) during a Phase 1b study evaluating bNAb safety, tolerability, and efficacy in combination with the HIV capsid inhibitor lenacapavir (LEN) dosed every 6 months in antiretroviral therapy (ART)-suppressed people with HIV. (See oral presentation #193, Eron et al)

Methods

Figure 1. Study Design

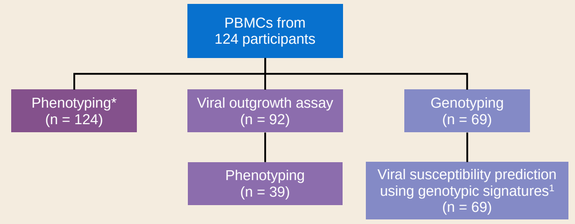


- Randomized, blinded Phase 1b study assessing safety and efficacy of a long-acting regimen LEN + teropavimab + zinlirvimab administered in 2 different doses.
- For study design details, please refer to oral presentation #193, Eron et al.

- Peripheral blood mononuclear cells (PBMCs) from 124 participants were collected at screening and used to assess susceptibility to teropavimab and zinlirvimab using 3 different methods (**Figure 2**).
- Phenotypic analysis of proviruses from PBMCs was performed using the PhenoSense mAb DNA assay (Monogram Biosciences; **Figure 3a**). Briefly, proviral DNA was extracted and the Env gene cloned into an Env-expression vector. Teropavimab and zinlirvimab were titrated against generated pseudoviruses to determine the IC_{90} of virus neutralization.
- Viral outgrowth (Accelevir Diagnostics) was performed on isolated PBMCs (**Figure 3b**). Outgrowth viruses with concentrations ≥ 1000 copies/mL were phenotyped using the PhenoSense mAb RNA assay (Monogram Biosciences) as described above.
- The HIV Env gene from proviral DNA in PBMCs was genotyped using deep sequencing via the MiSeq platform (Seq-IT; **Figure 3c**).
- Previously developed genotypic signatures were used to determine genotypic susceptibilty.[1] Briefly, neutralization data combined with virus sequence information derived from CATNAP[2] and an internal Gilead database were used to identify HIV Env amino acid positions important for susceptibility to teropavimab and zinlirvimab. Sequence variability was evaluated per participant and amino acid position. Only positions with variability < 1% in viral quasispecies were considered part of a signature.

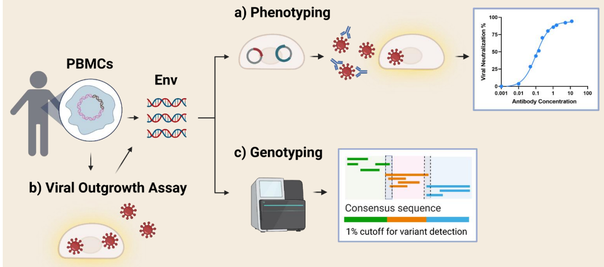
Methods (cont'd)

Figure 2. Screening Overview



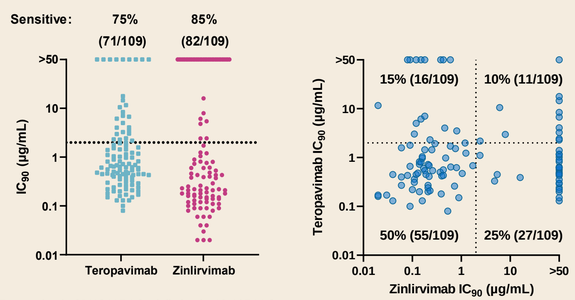
*Required for enrollment.

Figure 3. Screening Assays



Results

Figure 4. Distribution of bNAb PhenoSense mAb DNA Assay IC_{90} Values in Screened Participants

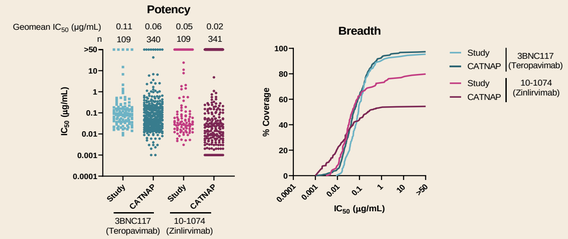


Teropavimab, 3BNC117-LS; zinlirvimab, 10-1074-LS.
Susceptibility defined as $IC_{90} \leq 2$ μg/mL.

- PhenoSense assay results were obtained for 109 of 124 screened participants, resulting in an overall failure rate of 12%.
- 75% (IC_{90} geometric mean: 0.73 μg/mL) and 85% (IC_{90} geometric mean: 0.26 μg/mL) of participants had an $IC_{90} \leq 2$ μg/mL to teropavimab and zinlirvimab, respectively.
- 50% (55 of 109) of participants had an $IC_{90} \leq 2$ μg/mL to both bNAbs.
  - 90% (98 of 109) had an $IC_{90} \leq 2$ μg/mL for one of the bNAbs.

Results (cont'd)

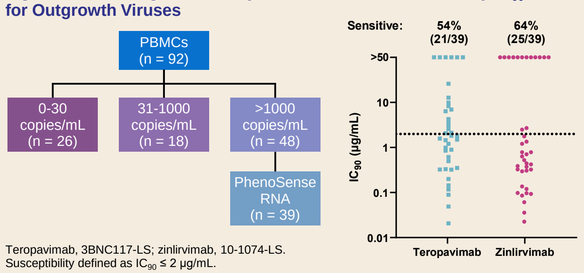
Figure 5. Comparison of bNAb PhenoSense mAb DNA Assay Data to Potency and Breadth Reported in CATNAP[2] Database



All CATNAP data for clade B viruses.

- The IC_{50} geometric mean of teropavimab (0.11 μg/mL) and zinlirvimab (0.05 μg/mL) are similar to those reported for 3BNC117 (0.06 μg/mL) and 10-1074 (0.02 μg/mL) in CATNAP.[2]
- The breadth of teropavimab (95%) is similar to that of 3BNC117 (97%) reported in CATNAP,[2] while zinlirvimab shows a higher breadth (80%) than reported for 10-1074 (54%) in CATNAP.[2]

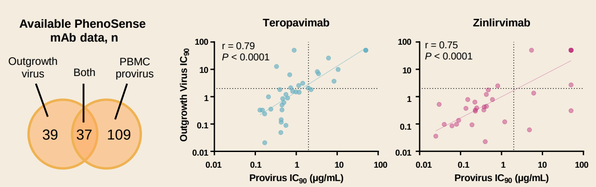
Figure 6. Viral Outgrowth Assay and PhenoSense mAb Assay IC_{90} Values for Outgrowth Viruses



Teropavimab, 3BNC117-LS; zinlirvimab, 10-1074-LS.
Susceptibility defined as $IC_{90} \leq 2$ μg/mL.

- 39 of 48 participant samples with viral outgrowth of ≥ 1000 copies/mL were successfully phenotyped.
- 54% and 64% of participants' outgrowth viruses had an $IC_{90} \leq 2$ μg/mL to teropavimab and zinlirvimab, respectively.

Figure 7. Correlation of PhenoSense mAb Assay IC_{90} Values for Provirus and Outgrowth Virus



Teropavimab, 3BNC117-LS; zinlirvimab, 10-1074-LS.
Susceptibility defined as $IC_{90} \leq 2$ μg/mL.

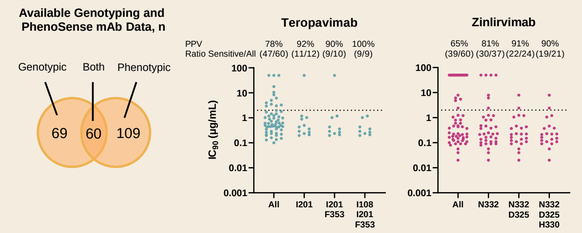
- For 37 participant samples, both phenotypic susceptibility data for outgrowth and PBMC provirus were available.
- IC_{90} values for proviruses and outgrowth viruses were well correlated showing r-values of r = 0.79 and r = 0.75 for teropavimab and zinlirvimab, respectively. 75% and 89% of participants had matching PhenoSense assay results for outgrowth or PMBC virus of $IC_{90} \leq 2$ μg/mL or $IC_{90} > 2$ μg/mL for teropavimab or zinlirvimab, respectively.

Table 1. Genotypic Signatures to Predict bNAb Susceptibility[1]

Teropavimab Env Amino Acid Positions	PPV (%)	Zinlirvimab Env Amino Acid Positions	PPV (%)
No signature	75	No signature	62
I201	78	N332	75
I201/F353	84	N332/D325	80
I108/I201/F353	86	N332/D325/H330	83

Positive predictive value (PPV), probability that a virus with a given signature is sensitive; analysis based on 203 subtype B viruses for elipovimab and 234 subtype B viruses for 3BNC117; HXB2 numbering used for HIV Env amino acid positions; N332, N332 glycan N-X-S/T.

Figure 8. Genotypic Prediction of Phenotypic Susceptibility



Teropavimab, 3BNC117-LS; zinlirvimab, 10-1074-LS. Susceptibility defined as $IC_{90} \leq 2$ μg/mL.
PPV = positive predictive value.

- For 60 participant samples, both genotypic and phenotypic susceptibility data were available.
- Proviral genotypic signatures predicted phenotypic susceptibility of proviruses and outgrowth virus with high PPV and specificity (93% to 100% teropavimab, 71% to 96% zinlirvimab), but low sensitivity.

Conclusions

- Three different methods to determine susceptibility to teropavimab and zinlirvimab in ART-suppressed participants were compared.
- Of 109 participants with PhenoSense DNA results, 50% had an $IC_{90} \leq 2$ μg/mL to both bNAbs and 90% for at least one bNAb.
- The potency and breadth of bNAbs measured by PhenoSense DNA were well correlated with those published in the CATNAP database.
- Zinlirvimab demonstrated greater breadth in our study as compared to that reported for 10-1074 (clade B viruses) in the CATNAP database.
- Phenotypic susceptibilities determined for proviruses and outgrowth virus are well correlated.
- Genotypic signatures predict phenotypic susceptibility with high specificity but low sensitivity, suggesting that they may aid in identifying people with virus susceptible to teropavimab and zinlirvimab.
- These data demonstrate a good correlation between the 3 assays: phenotyping, genotyping, and viral outgrowth in combination with phenotyping. Each assay may have a role in identifying people who can be treated with bNAbs.

References: 1. Moldt B, et al. *J Acquir Immune Defic Syndr.* 2021;88:61-9.
2. Yoon H, et al. *Nucleic Acid Res.* 2015;43:W213-W219.

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