Correlation of Baseline Phenotypic Sensitivity With Virologic Response to VH3810109 (N6LS) in BANNER

P037

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Key Takeaways

- **Baseline VH3810109 (N6LS) phenotypic sensitivity was broad and correlated with magnitude and duration of antiviral response**
- **During monotherapy, an evolution of virus toward reduced sensitivity to N6LS was observed, with no further provirus evolution to reduced N6LS sensitivity over 48 weeks of suppressive standard-of-care (SOC) antiretroviral therapy (ART) and a trend toward reversion to baseline sensitivity**
- **Most participants (81%) with successful phenotypic testing met protocol-defined N6LS sensitivity criteria required for enrollment in the ongoing phase 2b study**

Introduction

- VH3810109 (N6LS) is a broadly neutralizing CD4-binding site antibody being developed for long-acting HIV-1 therapy
- N6LS was well tolerated and demonstrated robust antiviral efficacy in people with HIV-1 when administered intravenously (IV) or subcutaneously (SC) in the proof-of-concept phase 2a BANNER study[1-4]
  - Antiviral activity correlated with N6LS exposure, with a maximum viral nadir from baseline of −2.60 $\log_{10}$ c/mL[2-4]
- Pre-treatment viral susceptibility testing may guide N6LS use; therefore, we compared phenotypic sensitivity in HIV-1 RNA and proviral DNA before and after N6LS monotherapy and in proviral DNA before and after 48 weeks of viral suppression on SOC ART

Methods

- The BANNER study assessed N6LS safety, pharmacokinetics, and antiviral activity in adults naive to ART. N6LS was evaluated during monotherapy after single-dose administration (IV or SC), followed by 48 weeks of SOC ART (Figure 1)
- Plasma viral RNA and proviral DNA antibody sensitivity was determined retrospectively using the PhenoSense® mAb assay (Monogram Biosciences)
- Exposure-response (ER) modeling was performed for maximum decline in plasma HIV-1 RNA and N6LS exposure metrics, and the impact of baseline in vitro sensitivity to N6LS (IC_{50}, IC_{80}, IC_{90}, IC_{95}) on antiviral effect was assessed
- Analyses were performed post hoc; Fisher's exact test evaluated associations between categorical variables, and Pearson's correlation assessed linear relationships between continuous variables

Results

- 62 participants were enrolled in BANNER
  - N6LS phenotyping was successful using plasma viral RNA for n=54 participants at baseline and n=56 at SOC initiation and using proviral DNA for n=45 participants at baseline, n=44 at SOC initiation, and n=38 at 48 weeks after SOC initiation

Baseline Phenotypic Sensitivity

- Pre-treatment viral RNA sensitivity to N6LS was broad, with IC_{90} values ranging from 0.09 to >50 µg/mL
- 81% (44/54) of participants had N6LS IC_{90} ≤2 µg/mL and maximum percent inhibition (MPI) >98% at baseline (Figure 2)
- There was no association between phenotypic sensitivity (IC_{90} ≤2 µg/mL and MPI >98% vs IC_{90} >2 µg/mL or MPI ≤98%) and sex, race, HIV-1 subtype, or CDC HIV stage (Table 1)
- An Emax model showed a clear ER relationship, with higher N6LS exposures resulting in greater VL declines
  - Baseline viral phenotypic sensitivity to N6LS was an important predictor of N6LS concentrations required to achieve antiviral effect (ie, participants with higher in vitro IC_{90} required higher N6LS exposure to achieve similar viral reduction compared with participants with lower in vitro IC_{90})
- In all ER models, in vitro phenotypic IC_{90} value was consistently the most strongly correlated with N6LS exposure achieving half-maximal effect (EC_{50}), compared with IC_{50}, IC_{80}, or IC_{95} values (Table 2)[4]

Correlation Between Baseline Sensitivity and Clinical Outcomes by Treatment

- Across all dose groups, weak-to-moderate correlations (Pearson's r = 0.4 to 0.7) were observed between lower N6LS IC_{90} at baseline and greater maximum VL decline (Figure 3A)
- Weak-to-moderate correlations (r = −0.3 to −0.8) between lower baseline N6LS IC_{90} and longer time to rebound were also observed for all dose groups, except 70 mg IV (Figure 3B)

Assessment of Baseline Log_{10} VL and CD4+ T-cell Count

- Correlations between baseline $\log_{10}$ VL and CD4+ T-cell count with virologic outcomes were dependent on drug exposure
  - In the 280 mg IV and 700 mg IV dose groups, weak correlations (r = −0.3 to −0.5) between lower baseline $\log_{10}$ VL and longer time to rebound were observed
  - In the 40 mg/kg IV and 280 mg IV dose groups, higher baseline CD4+ T-cell count showed weak-to-moderate correlations with greater maximum VL decline (r = −0.3 to −0.7) and longer time to rebound (r = 0.7 to 0.8)

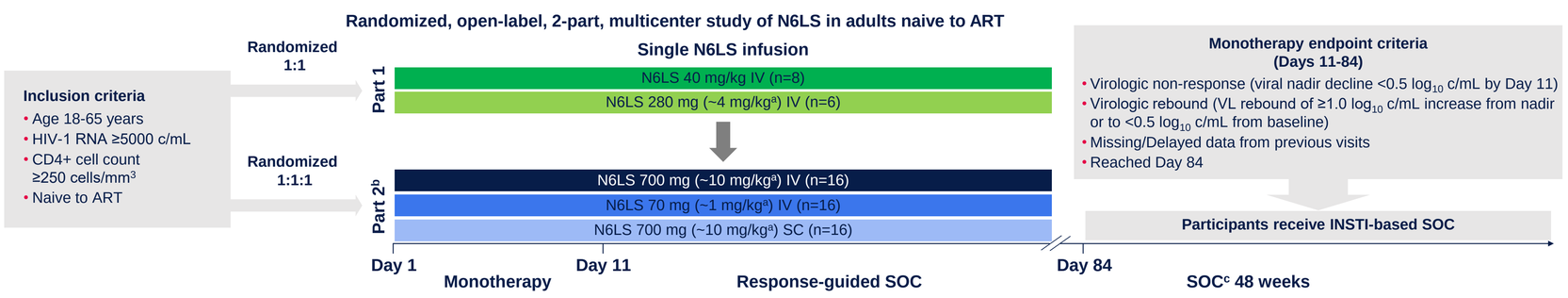
Distribution of N6LS IC_{90} and Correlation Between Plasma Viral RNA and Proviral DNA

- As shown in Figure 4, there was an evolution of virus from baseline to SOC initiation toward reduced sensitivity to N6LS
- For proviral DNA, no further evolution (≤3-fold change in IC_{90}) to decreased N6LS sensitivity from SOC initiation to 48 weeks after SOC initiation was observed, with a trend toward reversion to baseline sensitivity (Figure 4B)
- IC_{90} values between plasma viral RNA and proviral DNA were well correlated at baseline and SOC initiation with r values of 0.953 and 0.602 (Figure 5A-B); IC_{90} values were well correlated (r = 0.790) between proviral DNA at SOC initiation and at SOC Week 48 (Figure 5C)

Conclusions

- Baseline N6LS viral sensitivity correlated with magnitude and duration of antiviral response, which were related to dose and resulting N6LS exposure
- In vitro phenotypic IC_{90} value was consistently the most strongly correlated with N6LS exposure achieving EC_{50}
- During monotherapy, an evolution of virus toward decreased sensitivity to N6LS was observed in both blood (plasma viral RNA) and lymphocytes (proviral DNA); no further evolution to decreased N6LS sensitivity was observed in proviral DNA over 48 weeks of suppressive ART, with a trend toward reversion to baseline sensitivity
- Overall, 81% of participants with successful phenotypic testing met protocol-defined N6LS sensitivity criteria required for enrollment in the ongoing phase 2b study (EMBRACE, NCT05996471)

Figure 1. Study Design



[a]For a 70-kg individual. [b]Part 2, with doses described, was triggered after a planned interim analysis of part 1 data was performed and demonstrated acceptable virologic response, safety, and pharmacokinetics from the monotherapy and SOC periods. [c]An SOC INSTI-based regimen (dolutegravir/lamivudine) was provided at the end of the monotherapy periods in parts 1 and 2.

Figure 2. Distribution of Pre-dose Viral RNA Sensitivity (IC_{50}, IC_{80}, and IC_{90} µg/mL and MPI) to N6LS

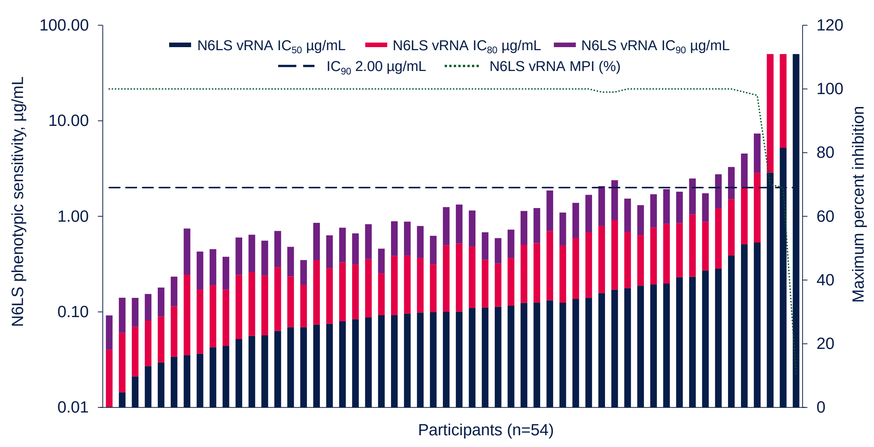


Table 1. Participant Characteristics by Baseline Viral RNA Phenotypic Sensitivity

Characteristic, n (%)	N6LS IC_{90} ≤2 µg/mL and MPI >98% (N=44)	N6LS IC_{90} >2 µg/mL or MPI ≤98% (N=10)	*P* value[a]
Sex			1.0000
Male	40 (91)	10 (100)	
Female	4 (9)	0	
Race			0.5615
Black or African American	9 (20)	1 (10)	
White, Caucasian, or European	30 (68)	7 (70)	
Other races[b]	5 (11)	2 (20)	
HIV-1 subtype			0.2045
B	23 (52)	6 (60)	
C	3 (7)	1 (10)	
BF	11 (25)	0	
Other/Missing[c]	7 (16)	3 (30)	
CDC HIV classification			0.6951
Stage 0	4 (9)	0	
Stage 1	19 (43)	7 (70)	
Stage 2	19 (43)	3 (30)	
Stage 3	2 (5)	0	
Age, median (range), y	28.0 (18-61)	31.5 (25-51)	Pearson's r (90% CI): −0.06 (−0.279, 0.172)[d]

[a]2-sided *P* value, Fisher's exact test. [b]Included American Indian or Alaska Native (n=2), Native Hawaiian or Other Pacific Islander (n=1), and individuals of multiple races (n=4). [c]Included AE, AG, AG/B, and D (n=1 each), complex (n=2), and missing (n=4). [d]Correlation between ungrouped baseline viral RNA susceptibility ($\log_e$ IC_{90}) and age (y).

Table 2. Rank Order of Covariate Effect of In Vitro Baseline IC Values and EC_{50} Parameter in ER Models[4]

ER model	IC_{50}	IC_{80}	IC_{90}	IC_{95}
Concentration at maximum VL decline	4	3	1	2
Cmax	4	3	1	2
Cavg based on AUC_{0-14}	4	2	1	3

AUC_{0-14}, area under the concentration–time curve from 0 to 14 days; Cavg, average concentration; Cmax, maximum concentration.

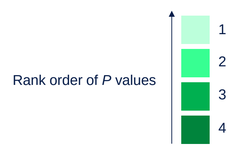
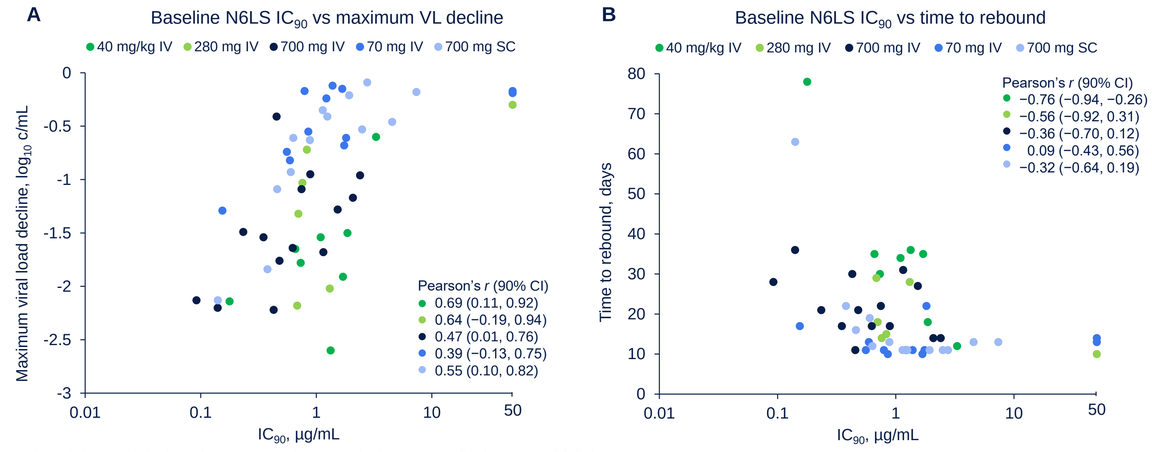
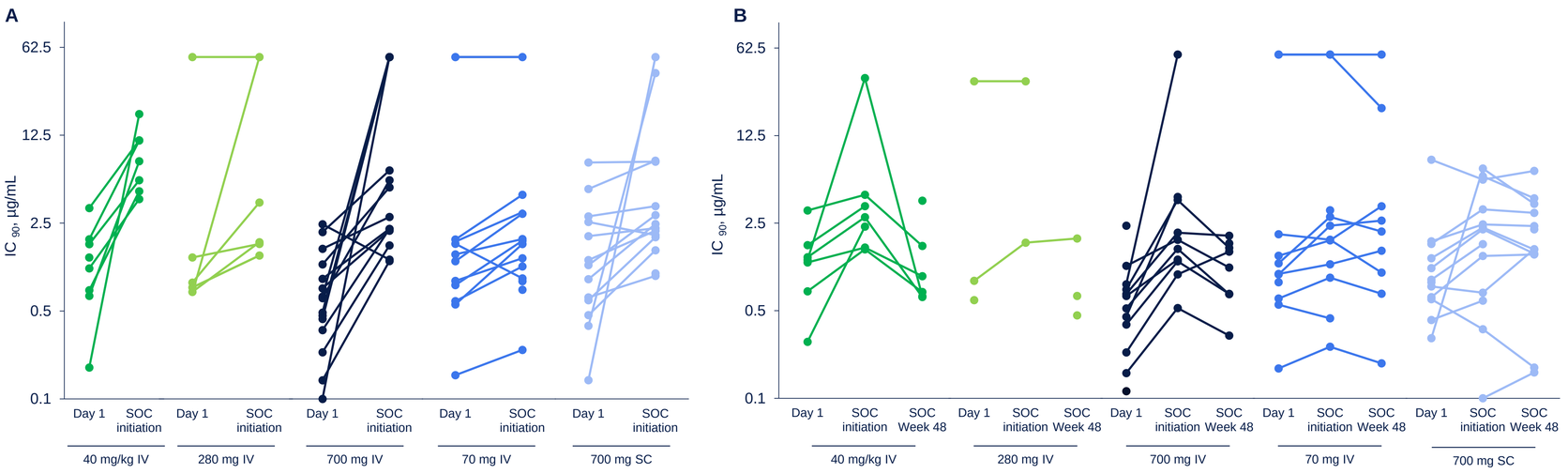


Figure 3. (A) Maximum VL Decline and (B) Time to Rebound by Baseline N6LS IC_{90}[a]



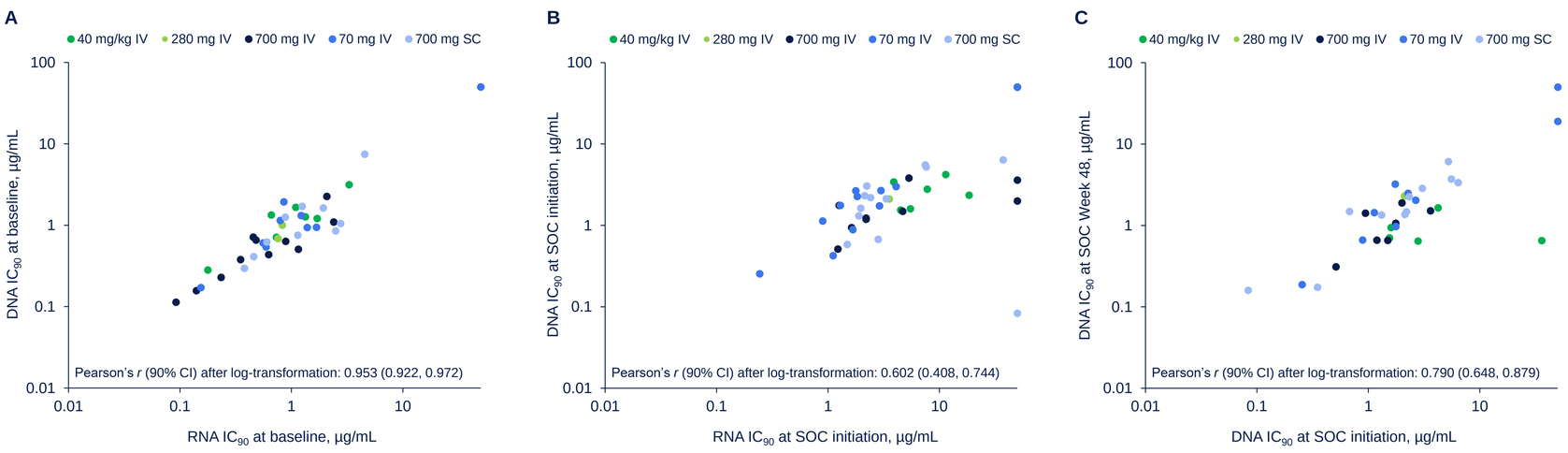
[a]50 µg/mL was the highest drug concentration tested in the assay; >50 is imputed to 50.001.

Figure 4. Distribution of N6LS IC_{90} in (A) Plasma Viral RNA and (B) Proviral DNA[a]



[a]50 µg/mL was the highest drug concentration tested in the assay; >50 is imputed to 50.001.

Figure 5. Correlation Between Plasma Viral RNA and Proviral DNA at (A) Baseline and (B) SOC Initiation and (C) Correlation Between Proviral DNA at SOC Initiation and 48 Weeks After SOC Initiation[a]



[a]50 µg/mL was the highest drug concentration tested in the assay; >50 is imputed to 50.001.

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