Pharmacokinetics/Pharmacodynamics and Virological Activity of VH3810109 (N6LS) in Antiretroviral-Naive Viremic Adults From the Phase 2a BANNER Study

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Key Takeaways

- **A population pharmacokinetic/pharmacodynamics (PK/PD) model was developed to evaluate the relationship between VH3810109 (N6LS) PK and PD in antiretroviral therapy (ART)-naive viremic adults**
- **Robust antiviral activity was observed after intravenous (IV) and subcutaneous (SC) administration of N6LS and response was correlated with exposure, demonstrating a favorable PK/PD profile for N6LS dosed either IV or SC**

Introduction

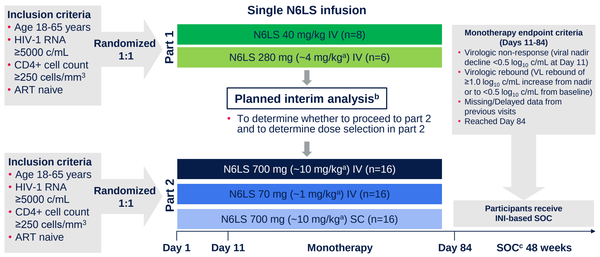
- Broadly neutralizing antibodies (bNAbs) are under development for both the treatment and prevention of HIV-1
- N6LS is a novel bNAb targeting the CD4-binding site of the HIV-1 envelope, which shows broad and potent neutralization activity in vitro, and has demonstrated robust antiviral effect in adults living with HIV-1[1]
- N6LS PK has been evaluated in 2 healthy participant studies (VRC 609 and 217901 [SPAN]) and in a phase 2a study (207959 [BANNER]) in ART-naive adults living with HIV-1
- Here we developed a population PK (popPK) model to describe the PK of N6LS in both healthy and viremic adults following single and multiple doses and evaluated the relationship between N6LS PK and changes in viral load in the BANNER study
- The aim of this work was to understand the impact of N6LS exposure on antiviral effect and to assess which factors influence the amount of N6LS required to achieve reduction in viral load

Methods

Study Design

- Data from 3 studies were included in the development of the N6LS popPK model:
  - VRC 609, a phase 1 first-time-in-human study in 22 participants that assessed single doses (5, 20, and 40 mg/kg given intravenously [IV] and 5 mg/kg given subcutaneously [SC]) and multiple doses (20 mg/kg IV and 5 mg/kg SC given every 12 weeks, 3 doses in total) of N6LS
  - SPAN, a phase 1 study in 24 participants that assessed single doses (60 mg/kg IV, and 20 mg/kg and 3000 mg SC with recombinant human hyaluronidase PH20 [rHuPH20], an agent that facilitates SC delivery of co-administered therapeutics through increased absorption and dispersion[2,3])
  - BANNER, a phase 2a study in 62 participants as described in Figure 1
- Data from BANNER were included in the PK/PD modeling and exposure-response (ER) assessment
- HIV-1 envelopes derived from pre-treatment plasma were tested for phenotypic sensitivity to N6LS using the PhenoSense® mAb RNA assay (Monogram Biosciences, South San Francisco, CA)

Figure 1. BANNER Study Design

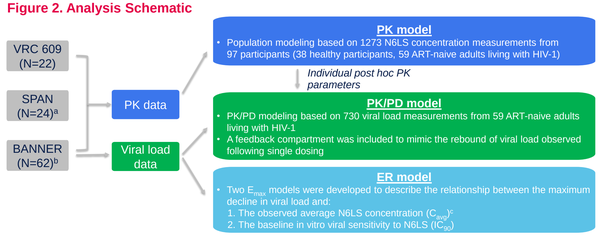


ART, antiretroviral therapy; INI, integrase inhibitor; IV, intravenous; SC, subcutaneous; SOC, standard of care; VL, viral load. [a]For a 70-kg individual. [b]A planned interim analysis was performed to evaluate virologic response, safety, and pharmacokinetics from the monotherapy and SOC periods in part 1. [c]A SOC INI-based regimen (dolutegravir/lamivudine) was provided at the end of the monotherapy periods in parts 1 and 2.

Analysis

- The analysis approach is described in Figure 2
- The impact of the following factors on antiviral effect was assessed: individual baseline viral load, baseline in vitro viral sensitivity (IC_{50} and IC_{90}), and baseline CD4+ cell count
  - Sensitivity analysis was also carried out excluding participants who had baseline in vitro IC_{50} values >0.25 µg/mL
- PopPK and PK/PD modeling was performed in NONMEM (version 7.4) and ER in R (version 4.0.5)

Figure 2. Analysis Schematic



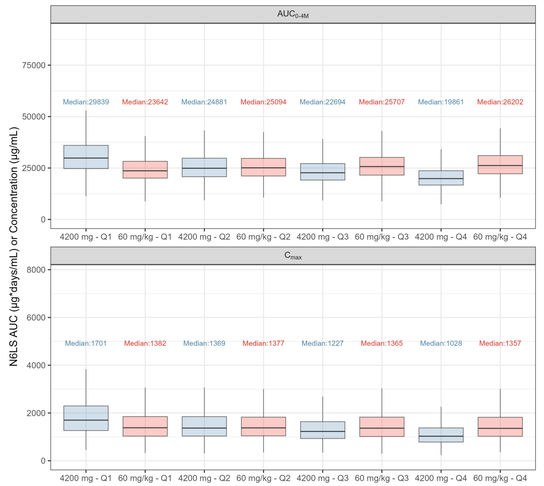
ART, antiretroviral therapy; ER, exposure response; PD, pharmacodynamic; PK, pharmacokinetic. [a]PK data from 16 participants were available at the time of the analysis. [b]Data from 3 participants were excluded due to dosing error. [c]Calculated as the area under the concentration time curve over 14 days (AUC_{0-14})/14 days.

Results

PopPK Analysis

- N6LS PK was well described by a 2-compartment model with linear elimination and first-order SC absorption
- ART-naive participants showed 30% faster clearance than healthy participants, resulting in a lower exposure in ART-naive participants compared with healthy participants for the same N6LS dose; based on data from other bNAbs, it would be expected that suppressed individuals would have PK more similar to that of healthy participants[4-7]
- A higher SC N6LS exposure was obtained when rHuPH20 was present: co-administration of rHuPH20 increased the SC relative bioavailability by 57%
- Body weight was identified as having an impact on PK, which is typical for antibodies; standard allometric scaling exponents were included in the popPK model on clearance and volume parameters
  - Minimal impact of body weight on N6LS exposure was observed; Figure 3 demonstrates the overlap in the range of N6LS exposures expected when dosing flat dose versus mg/kg dosing

Figure 3. Box and Whisker Plots Showing Simulated AUC and C_{max} Values for a Single N6LS IV Dose of 60 mg/kg or 4200 mg by Body Weight Quartile

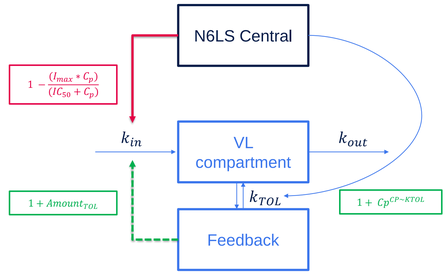


Body weight quartile (Q) 1 = 22.5-65.0 kg; Q2 = 65.0-74.2 kg; Q3 = 74.2-83.9 kg; Q4 = 83.9-129.1 kg.

PK/PD Analysis

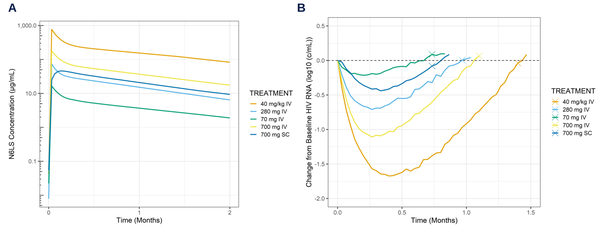
- Viral dynamic changes were adequately described by an indirect-response PK/PD model with an inhibitory E_{max} drug effect function (Figure 4)
- Decrease in viral load was demonstrated at all doses (Figure 5), with viral rebound occurring relatively rapidly after achieving nadir. It should be noted that this rebound was observed following single-dose administration; multiple doses are being assessed in the ongoing phase 2b study
- The model-predicted N6LS concentration required to achieve half-maximal effect was 96.3 µg/mL, which was consistent with the robust antiviral effect achieved with the higher doses in BANNER
- The PK/PD relationship between SC and IV was consistent; as expected, higher SC doses are needed to achieve comparable IV exposure

Figure 4. PK/PD Model Structure



Cp, concentration of N6LS; IC_{50}, concentration achieving half-maximal inhibition; I_{max}, maximal inhibition; K_{in}, rate of input; K_{out}, rate of output; K_{TOL}, rate of feedback; TOL, feedback; VL, viral load.

Figure 5. (A) Simulated Median PK Profile and (B) PK/PD Model Simulations of Median Change From Baseline in Viral Load Versus Time

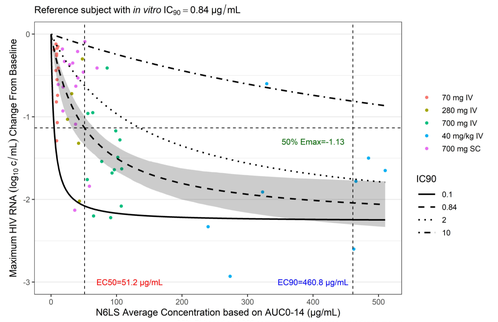


In the right panel, "X" marks observed median standard of care initiation time for the single IV and SC doses used in BANNER.

ER Analysis

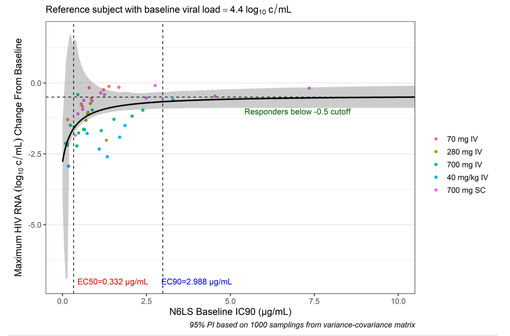
- N6LS C_{avg} concentration as the driver of effect (Figure 6):
  - There was a high correlation between N6LS exposure and effect; higher N6LS exposure was associated with a larger decline in viral load
  - Baseline viral sensitivity to N6LS was an important predictor of N6LS concentrations required to achieve antiviral effect, i.e., participants with a higher in vitro IC_{90} required higher N6LS exposure to achieve a similar viral reduction compared with participants with a lower in vitro IC_{90}
  - Baseline viral load and baseline CD4+ cell count were not predictive of effect
- In vitro baseline IC_{90} as the driver of effect (Figure 7):
  - Higher baseline IC_{90} values were associated with a lower reduction in viral load; participants with a baseline IC_{90} of 0.332 µg/mL would be expected to achieve 50% of the typical maximum effect whereas those with a baseline IC_{90} of ~3 µg/mL would only achieve 10% of the typical maximum effect
  - Baseline CD4+ cell count was not predictive of effect

Figure 6. ER Relationship Between N6LS C_{avg} and Maximum HIV-1 RNA Change From Baseline and Impact of Different In Vitro Baseline IC_{90} Values



Solid and dashed curves: E_{max} model fit based on various IC_{90} values; shaded region: 95% prediction interval for the reference population; vertical dashed lines: exposures required to achieve 50% and 90% of maximal effect. EC_{50}, exposure achieving half-maximal effect; EC_{90}, exposure achieving 90% of maximal effect.

Figure 7. ER Relationship Between In Vitro Baseline IC_{90} Values and Maximum HIV-1 RNA Change From Baseline



Solid line: E_{max} model fit; shaded region: 95% prediction interval; vertical dashed lines: exposures required to achieve 50% and 90% of maximal effect. Horizontal dashed line: 0.5 log viral load change from baseline; figure truncated at IC_{90} of 10 µg/mL. EC_{50}, IC_{90} associated with half-maximal effect; EC_{90}, exposure associated with 10% of maximal effect.

Conclusions

- Robust antiviral activity was observed following IV and SC administration of N6LS in the phase 2a BANNER study and the effect was correlated with N6LS exposure
- The relationship between N6LS concentration and change in viral load was consistent between SC and IV; however, as expected, the exposure achieved with SC was lower than with IV, hence higher SC doses are required to achieve a similar antiviral effect
- Co-administration of rHuPH20 increased the SC relative bioavailability by 57% and could therefore be used to achieve higher exposures of N6LS following SC administration in future studies
- Baseline viral sensitivity to N6LS impacts the amount of N6LS required to achieve effect; participants with high in vitro sensitivity (i.e., low baseline in vitro IC_{90}) require a lower N6LS dose than participants with low in vitro sensitivity to achieve a similar viral load reduction
- Participants with high in vitro sensitivity are more likely to achieve a larger decline in viral load
- This modeling demonstrates N6LS has a favorable PK/PD profile whether administered IV or SC and has been successfully applied to support dose selection for the ongoing phase 2b study
- Additional data on the safety of N6LS from the BANNER study are presented in Slides PS8.O5[8]

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References: 1. Leone et al. HIV Drug Therapy Glasgow 2022; Glasgow, Scotland. Slides O34. **2.** Locke et al. *Drug Deliv.* 2019;26:98-106. **3.** Morcos et al. *Int J Clin Pharmacol Ther.* 2013;51:537-548. **4.** Caskey et al. *Nature.* 2015;522:487-491. **5.** Caskey et al. *Nat Med.* 2017;23:185-191. **6.** Caskey et al. CROI 2022; Virtual. Abstract 140. **7.** Mendoza et al. *Nature.* 2018;561:479-484. **8.** Leone et al. EACS 2023; Warsaw, Poland. Slides PS8.O5.

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