Pharmacokinetics/Pharmacodynamics and Exposure-Response Modelling of VH3810109 (N6LS) in Antiretroviral Therapy-Naive Adults With HIV-1 From the Phase 2a BANNER Study

I-096

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Key Takeaways

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

Introduction

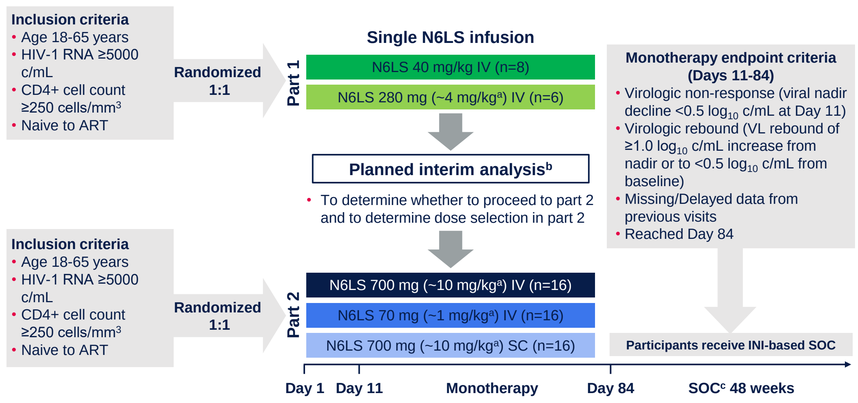
- Broadly neutralizing antibodies (bnAbs) are under development for both the treatment and prevention of HIV-1
- VH3810109 (N6LS) is a novel bnAb targeting the CD4-binding site of the HIV-1 envelope, which shows broad and potent neutralization activity in vitro, and has demonstrated robust antiviral effect in adults living with HIV-1[1-3]
- N6LS pharmacokinetics (PK) has been evaluated in 2 studies of HIV-negative participants (VRC 609 and 217901 [SPAN]) and in a phase 2a study (207959 [BANNER]) in adults living with HIV-1 naive to antiretroviral therapy (ART)
- Here we developed a population PK (popPK) model to describe the PK of N6LS in both HIV-negative and adults with viraemia following single and multiple doses, and evaluated the relationship between N6LS PK and exposure on antiviral effect in adults with viraemia
- The aim of this work was to understand the impact of N6LS exposure on antiviral effect and to assess which factors, including in vitro plasma viral RNA phenotypic sensitivity, 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 HIV-negative 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 HIV-negative participants that assessed single doses (60 mg/kg IV, and 20 mg/kg and 3000 mg SC, both administered with recombinant human hyaluronidase PH20 [rHuPH20], an agent that facilitates SC delivery of co-administered therapeutics through increased absorption and dispersion[4,5])
  - BANNER, a phase 2a study in 62 participants living with HIV-1 as described in Figure 1
- Data from BANNER were included in the PK/PD modelling and exposure-response (ER) assessment
- HIV 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

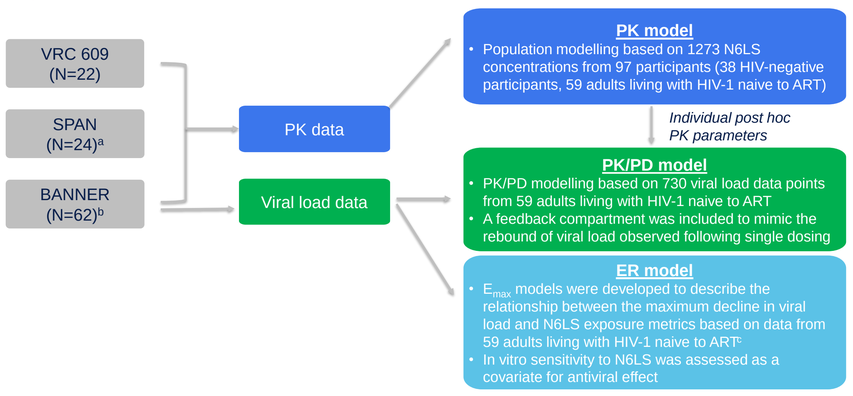


ART, antiretroviral therapy; INI, integrase inhibitor; IV, intravenous; SC, subcutaneous; SOC, standard of care; VL, viral load. [a]For a 70-kg individual. [b]A planned interim analysis was performed to evaluate virologic response, safety, and pharmacokinetics from the monotherapy and SOC periods in 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 antiviral activity of N6LS was evaluated using both a PK/PD modelling approach and an ER modelling approach. The analysis schematic is described in Figure 2
- ER modelling was performed based on the observed trends between maximum decline in plasma HIV-1 RNA during monotherapy and various exposure metrics, including N6LS concentration at the time of the maximum decline in plasma HIV-1 RNA, maximum N6LS concentration (C_{max}), and average N6LS concentration (C_{avg}) based on $AUC_{0\text{-}14}$
- The impact of the following factors on antiviral effect was assessed: individual baseline viral load, baseline in vitro sensitivity to N6LS (PhenoSense mAb RNA assay: IC_{50}, IC_{80}, IC_{90}, IC_{95}), and baseline CD4+ cell counts
  - Sensitivity analysis was also carried out excluding participants who had baseline in vitro IC_{50} values >0.25 µg/mL
- PopPK and PK/PD modelling was performed in NONMEM (Version 7.4) and ER in R (Version 4.0.5)

Figure 2. Analysis Schematic



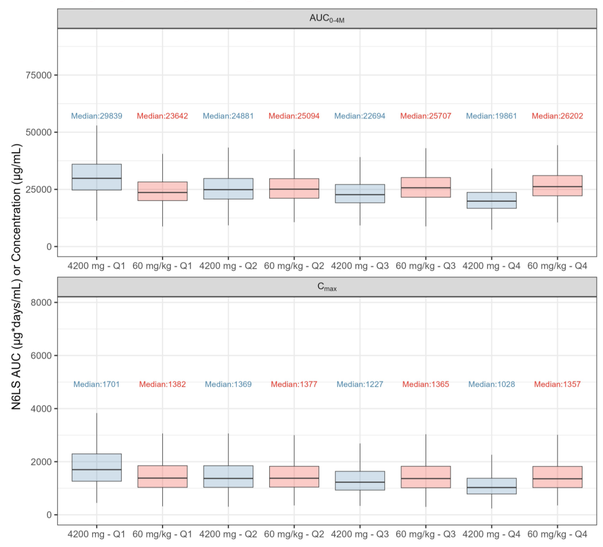
ART, antiretroviral therapy; ER, exposure response; PD, pharmacodynamic; PK, pharmacokinetic. [a]PK data from 16 participants were available at the time of the analysis. [b]Data from 3 participants were excluded due to dosing error. [c]C_{avg} ER model included data from 57 participants due to missing $AUC_{0\text{-}14}$ data in 2 participants.

Results

PopPK Analysis

- N6LS PK was well described by a 2-compartment model with linear elimination and first-order SC absorption
- Participants with viraemia showed 30% faster clearance than HIV-negative participants, resulting in a lower exposure in participants naive to ART compared with HIV-negative participants for the same N6LS dose; based on data from other bnAbs, it would be expected that participants with virologic suppression would have PK more similar to HIV-negative participants[6-9]
- 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 is 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

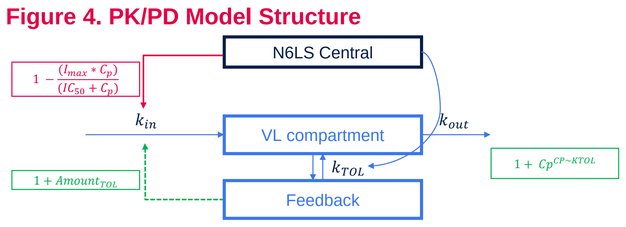


Body weight quartile (Q) 1 = 22.5-65.0 kg; Q2 = 65.0-74.2 kg; Q3 = 74.2-83.9 kg; Q4 = 83.9-129.1 kg.

PK/PD Analysis

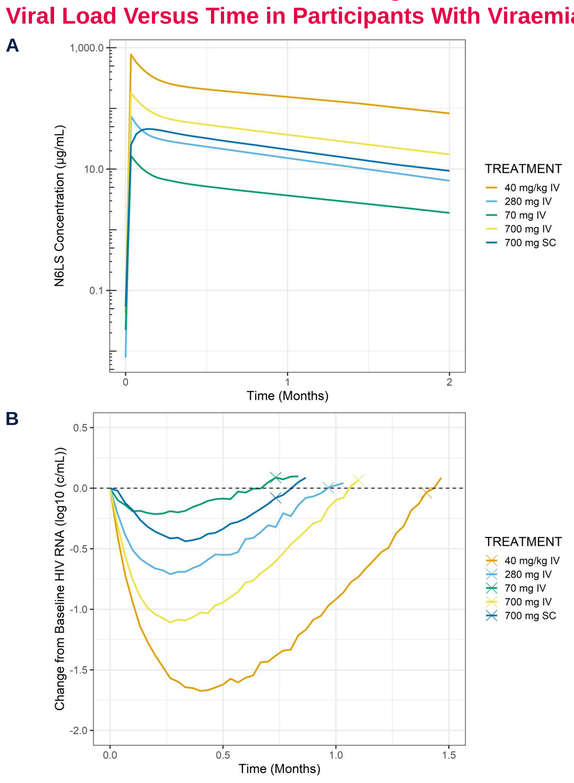
- Viral dynamic changes were adequately described by an indirect response PK/PD model with an inhibitory E_{max} drug effect function (Figure 4)
- Decrease in viral load was demonstrated at all doses (Figure 5), with viral rebound occurring relatively rapidly after achieving nadir. It should be noted 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 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 Participants With Viraemia

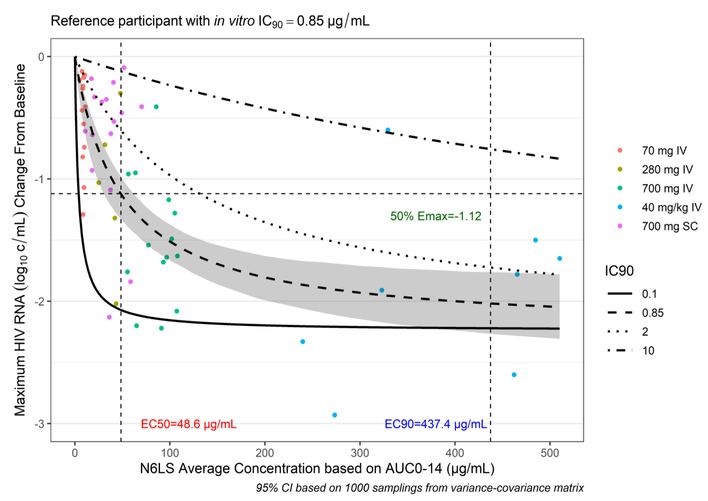


In Figure 5B, "X" marks observed median standard of care initiation time for the single IV and SC doses used in BANNER.

ER Analysis

- There was a high correlation between all evaluated N6LS exposure metrics and effect: higher N6LS exposure was associated with a larger decline in viral load
- A representative ER model with N6LS C_{avg} as the driver of effect was shown (Figure 6)
  - Baseline viral phenotypic 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 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 1), therefore supporting the rationale of using IC_{90} as a potential screening measure for phenotypic sensitivity
  - All 4 in vitro sensitivity measures were highly correlated with the EC_{50} (*P* value $<10^{-6}$ based on ANOVA testing comparing the covariate model with the base model)
  - Rank order of correlation with EC_{50}: $IC_{90} > IC_{80} \approx IC_{95} > IC_{50}$

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% confidence interval for the reference population; vertical dashed lines: exposures required to achieve 50% and 90% of maximal effect. CI, confidence interval; EC_{50}, exposure achieving half-maximal effect; EC_{90}, exposure achieving 90% of maximal effect; E_{max}, maximal effect.

Table 1. Rank Order of Covariate Effect of In Vitro Baseline IC Values and EC_{50} Parameter in ER Models

ER model	IC_{50}	IC_{80}	IC_{90}	IC_{95}
Concentration at maximum VL decline	4	3	1	2
C_{max}	4	3	1	2
C_{avg} based on $AUC_{0\text{-}14}$	4	2	1	3

Rank order of *P* values: 1, 2, 3, 4

$AUC_{0\text{-}14}$, area under the concentration–time curve from 0 to 14 days; C_{avg}, average concentration; C_{max}, maximum concentration; EC_{50}, exposure achieving half-maximal effect; IC, inhibitory concentration; VL, viral load.

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 and IC_{90} was the most predictive covariate of the ER relationship amongst susceptibility values; 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
- This modelling analysis demonstrates N6LS has a favourable PK/PD profile whether administered IV or SC and has been successfully applied to support dose selection for the ongoing phase 2b study (NCT05996471)

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