Population Pharmacokinetics, Antidrug Antibodies and Exposure-Response of VH3810109 (N6LS) in Virologically Suppressed Adults Living With HIV From the Phase 2b EMBRACE Study

MeP10.1

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Key Takeaways

- **We evaluated N6LS PK and its relationship to efficacy, safety, and ADA endpoints using ER analyses at Month 6 in the phase 2b EMBRACE study**
- **Multiple factors influenced viral outcomes at Month 6**
- **No relationship between ISRs and N6LS exposure was observed**
- **Minimal impact of body weight on exposure supports a switch from weight-based to flat dosing of N6LS**
- **Incidence of ADAs was low, with no impact on N6LS PK, efficacy, or safety**

Purpose

- Long-acting antiretroviral therapy (ART) offers convenient, sustainable solutions to improve quality of life and adherence and to combat the HIV epidemic
- VH3810109 (N6LS) is a broadly neutralizing CD4-binding site antibody in development for ultra-long-acting (ULA) HIV-1 treatment[1,2]
- N6LS is currently being investigated as a ULA (≥4-month dosing interval) antiretroviral option
- In the phase 2b EMBRACE study, N6LS was administered 60 mg/kg intravenously (IV) or 3000 mg subcutaneously (SC) with rHuPH20[a] every 4 months (Q4M) + monthly intramuscular long-acting cabotegravir (CAB LA) as a 2-drug regimen in adults with viral suppression
- A low occurrence of plasma HIV-1 RNA ≥50 c/mL at Month 6 was observed in EMBRACE
- We evaluated N6LS pharmacokinetics (PK) and its relationship to efficacy and safety endpoints through exposure-response (ER) analyses, including assessing the impact of antidrug antibodies (ADAs)

[a]rHuPH20, recombinant human hyaluronidase PH20, facilitates SC delivery of co-administered therapeutics through increased absorption and dispersion.[3,4]

Methods

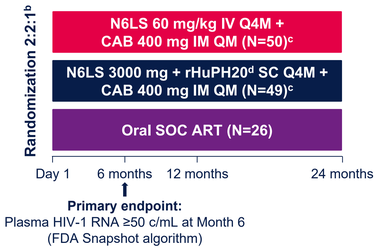
Study Design

- A previously reported population PK (popPK) model[5] (developed using data from 2 phase 1 studies in adult participants without HIV and a phase 2a study in people with HIV naive to ART) was updated with EMBRACE data through Month 6, and covariate effects were re-assessed
- The updated popPK model was used to generate individual exposure metrics for EMBRACE participants to assess the relationship between N6LS exposure and the following:
  - Proportion of participants with plasma HIV-1 RNA ≥50 c/mL up to and at Month 6 based on the FDA Snapshot algorithm
  - Incidence of infusion site reactions (ISRs) during the 6-month period
- Baseline characteristics, including phenotypic sensitivity to N6LS, and occurrence of ADAs were assessed to determine if there was any influence of these factors on ER
- The EMBRACE study design is described in Figure 1

Figure 1. EMBRACE Study Design

Key eligibility criteria

- Aged 18-70 years
- ≥2 HIV-1 RNA <50 c/mL in the 12 months before screening
- No prior ART switch due to VF
- CD4+ cell count ≥350 cells/mm^3
- On stable ART for ≥6 months
- No active HBV co-infection[a]
- Phenotypic sensitivity to N6LS (IC_{90} ≤2.0 µg/mL and MPI >98%)



ART, antiretroviral therapy; CAB, cabotegravir; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IC_{90}, 90% inhibitory concentration; IM, intramuscular; IV, intravenous; MPI, maximum percent inhibition; QM, every month; Q4M, every 4 months; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SOC, standard of care.
[a]Individuals positive for HBsAg or negative for HBsAg but positive for HBcAb with detectable HBV DNA were excluded. [b]Stratified by N6LS IC_{90} > or ≤1.0 µg/mL. [c]CAB 600 mg IM loading dose on Day 1. [d]rHuPH20 sourced from Halozyme Therapeutics, Inc (San Diego, CA).

Analysis

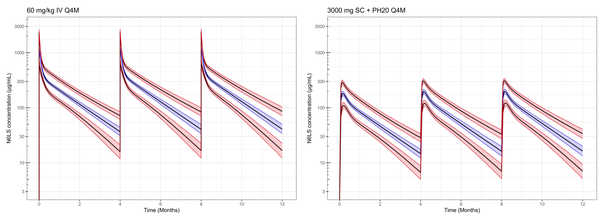
- Logistic regression modeling was used to characterize the ER relationship for efficacy and safety
- As the incidence of ISRs is expected to be dependent on the route of administration, IV and SC data were assessed separately in the safety ER
- PopPK modeling was performed in NONMEM (version 7.5.1) and ER in R (version 4.2.3)

Results

PopPK Analysis

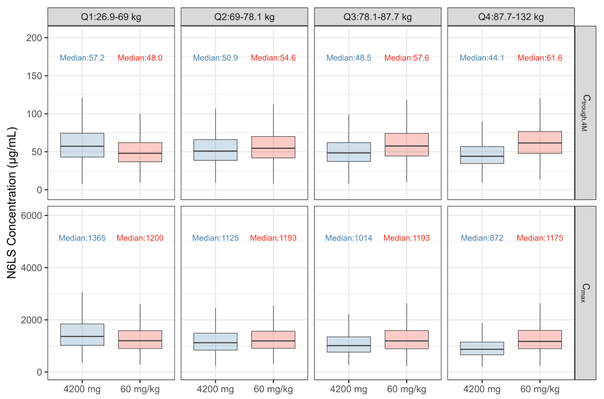
- N6LS PK was consistent with previous clinical studies
- As expected, N6LS exposures were higher with 60 mg/kg IV compared with 3000 mg + rHuPH20 SC (Figure 2)
- Simulations indicated minimal impact of body weight on exposure (Figure 3; 60 mg/kg and the equivalent flat dose for a 70-kg participant [4200 mg] are compared)

Figure 2. Simulated PK Profiles for N6LS 60 mg/kg IV Q4M and 3000 mg + rHuPH20 SC Q4M in a Virally Suppressed Population



CI, confidence interval; IV, intravenous; N6LS, VH3810109; PI, prediction interval; Q4M, every 4 months; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.
Black lines indicate the median, 5th, and 95th PIs. The blue band indicates the 95% CI around the median PI; red bands indicate the 95% CI around the 5th and 95th PIs.

Figure 3. Box and Whisker Plots Showing Simulated $C_{trough,4M}$ and C_{max} Values for N6LS 60 mg/kg or 4200 mg[a] IV Doses

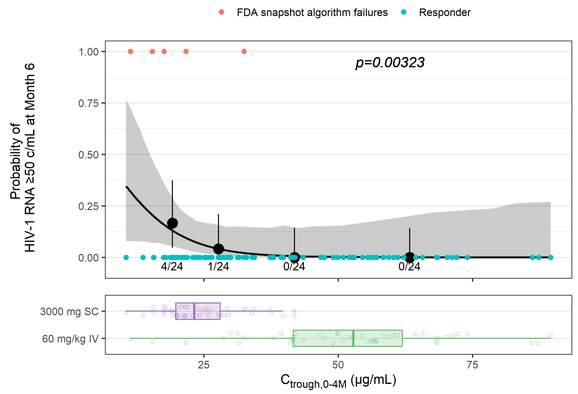


C_{max}, maximum concentration; $C_{trough,4M}$, trough concentration at Month 4; IV, intravenous; Qx, quartile x.
[a]4200 mg is 60 mg/kg for a 70-kg participant.
Median (minimum-maximum) weights: Q1 = 62.2 (26.9-69.0) kg; Q2 = 73.7 (69.0-78.1) kg; Q3 = 82.7 (78.1-87.7) kg; Q4 = 94.0 (87.7-132) kg.

ER Analysis

- Participants who had HIV-1 RNA ≥50 c/mL at Month 6 tended to have lower N6LS exposure (Figure 4); however, a reliable clinical threshold could not be established due to the small number with Snapshot HIV-1 RNA ≥50 c/mL observed (5/96 participants [5%])
- There was a trend for higher probability of HIV-1 RNA ≥50 c/mL in participants with detectable baseline viral load (>20 c/mL; Figure 5)
- There was no relationship between the occurrence of ISRs and N6LS exposure for the IV or SC groups (Figure 6; SC)

Figure 4. HIV-1 RNA ≥50 c/mL by $C_{trough,4M}$ (µg/mL) Quartiles at Month 6 (Based on FDA Snapshot Algorithm)



CI, confidence interval; $C_{trough,0-4M}$, minimum serum concentration at Month 4; CVF, confirmed virologic failure.
Notes: Colored circles at y = 0 represent participants with HIV-1 RNA <50 c/mL at Month 6 (responder), and colored circles at y = 1 represent participants with CVF (red; non-responder; defined as 2 consecutive HIV-1 RNA ≥200 c/mL) or Snapshot HIV-1 RNA ≥50 c/mL (turquoise). Black circles are the observed proportions of participants meeting the endpoint per exposure quartile, also shown as numerical values above the x-axis. Black vertical lines are the 95% CI of the probability of meeting an endpoint. Black curved lines are the linear logistic regression fit, and the gray shaded region represents the corresponding 95% CI. The *P* value is a likelihood ratio test comparing the logistic regression fit against the null hypothesis that the probability of response is independent of exposures. The box plot shows the exposures for the treatment groups.

Figure 5. Proportion of Participants With HIV-1 RNA ≥50 c/mL at Month 6 in Participants With Detectable Baseline VL (≥20 c/mL [≥1.3 log_{10} c/mL])

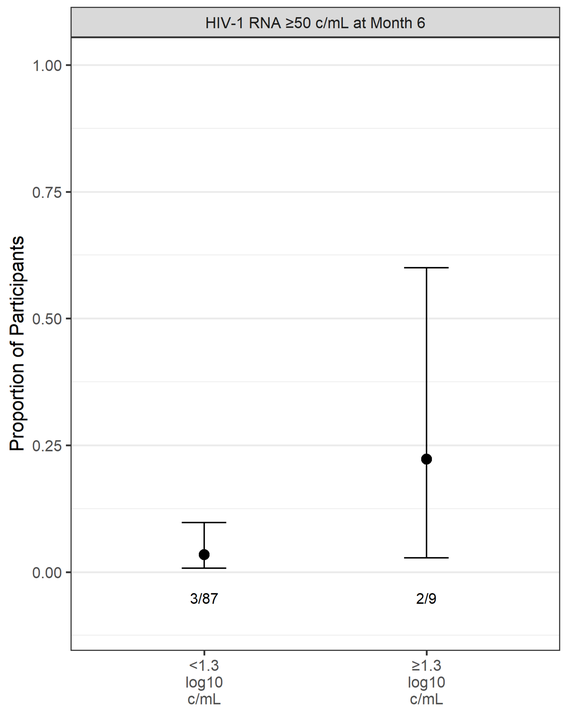
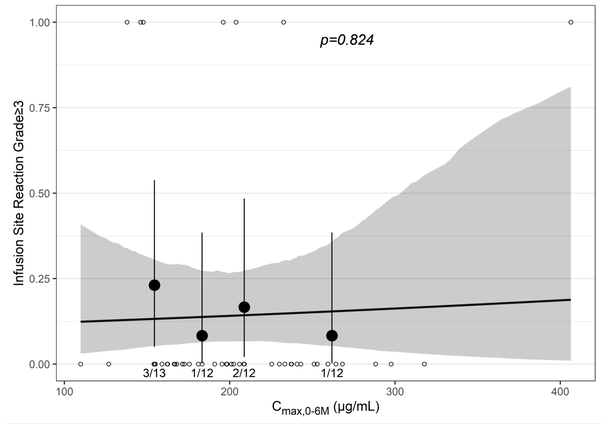


Figure 6. Probability of ISR Grade ≥3 Through Month 6 by $C_{max,6M}$ (µg/mL) Quartiles for N6LS 3000 mg + rHuPH20 SC Q4M



AE, adverse event; CI, confidence interval; $C_{max,0-6M}$, maximum serum concentration over 0-6 months; ISR, infusion site reaction; SC, subcutaneous.
Notes: Open circles at y = 0 represent participants without AEs, and open circles at y = 1 represent participants with AEs. Black circles are the observed proportions of AEs per exposure quartile. Black vertical lines are the 95% CI of the rate of AEs. The black line is the linear logistic regression fit, and the gray shaded region represents the corresponding 95% CI. The numbers above the x-axis represent the number of participants with ISR grade ≥3 out of the total number of participants within each exposure quartile for each age group.
No ISRs grade >1 were observed after administration of N6LS 60 mg/kg IV Q4M in EMBRACE.

Incidence of ADAs

- Incidence of ADAs was low (Table 1), with no impact of ADAs on N6LS PK, efficacy, or safety after assessment in the popPK and ER analyses

Table 1. Incidence of ADAs in EMBRACE

n, %	N6LS 60 mg/kg IV (N=50)	N6LS 3000 mg + rHuPH20 SC (N=49)
Participants with no ADAs	47 (94)	40 (82)
Participants with treatment-emergent ADAs	3 (6)	9 (18)

ADA, antidrug antibody; IV, intravenous; N6LS, VH3810109; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

Conclusions

- A low occurrence of plasma HIV-1 RNA ≥50 c/mL at Month 6 was observed in EMBRACE
- Participants who did not meet the efficacy endpoint tended to have lower N6LS exposure; however, N6LS exposure alone does not explain occurrence of CVF/Snapshot HIV-1 RNA ≥50 c/mL
- There was a trend for a higher probability of HIV-1 RNA ≥50 c/mL in participants with detectable baseline viral load (>20 c/mL)
- There was no relationship between ISRs and N6LS exposure for the IV or SC groups
- There was minimal impact of body weight on N6LS exposure; therefore, moving from mg/kg to flat dosing will have minimal impact on PK
- Incidence of ADAs was low, with no impact of ADAs on N6LS PK, efficacy, or safety
- This modeling (1) indicates multiple factors contribute to the observations of plasma HIV-1 RNA ≥50 c/mL at Month 6; (2) supports moving from mg/kg to flat IV dosing; and (3) demonstrates ADAs had no impact after Q4M dosing in participants with viral suppression
- For additional data on N6LS, please see Oral presentation PS09.1 and Posters eP127 and eP131[6-8]

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References: 1. Leone et al. HIV Drug Therapy Glasgow 2022; Glasgow, Scotland. Oral presentation O34. **2.** Leone et al. EACS 2023; Warsaw, Poland. Oral presentation PS8.O5. **3.** Locke et al. *Drug Deliv.* 2019;26:98-106. **4.** Morcos et al. *Int J Clin Pharmacol Ther.* 2013;51:537-548. **5.** Edwards et al. EACS 2023; Warsaw, Poland. Poster eP.A.099. **6.** Griesel et al. EACS 2025; Paris, France. Oral presentation PS09.1. **7.** Gartland et al. EACS 2025; Paris, France. Poster eP127. **8.** Gutner et al. EACS 2025; Paris, France. Poster eP131.

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