P-380

The Clinical Development of VH3810109 (N6LS): Advancing Ultra-Long-Acting HIV Treatment Into the Future

Peter Leone,[1] Paul Wannamaker,[1] Margaret Gartland,[1] Michael Warwick-Sanders,[2] Riccardo D'Agostino,[2] Rulan Griesel,[3] Chelsea Macfarlane,[1] Viviana Wilches,[4] Kathryn Brown,[5] Yash Gandhi,[4] David Dorey,[6] Gabriela L. Ghita,[4] Christina Donatti,[3] Babafemi Taiwo,[1] Sherene Min,[1] Jan Losos[1]

[1]ViiV Healthcare, Durham, NC, USA; [2]GSK, London, UK; [3]ViiV Healthcare, London, UK; [4]GSK, Collegeville, PA, USA; [5]Certara, Radnor, PA, USA; [6]GSK, Mississauga, Ontario, Canada

Presenting author:
Peter Leone
410 Blackwell Street
Durham, NC, USA 27701
peter.a.leone@viivhealthcare.com
1-919-483-7572

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Key Takeaways

- **VH3810109 (N6LS) is a broadly neutralizing CD4-binding site antibody in development for ultra-long-acting HIV-1 treatment**
- **N6LS has demonstrated high rates of virologic suppression as part of a complete long-acting (LA) regimen with cabotegravir (CAB) LA and a favorable safety and tolerability profile, particularly when administered intravenously (IV)**
- **Twice-yearly N6LS IV in combination with CAB LA is under evaluation for HIV-1 treatment**

Unmet Need for Complete Ultra-Long-Acting Regimen

- Lifelong adherence to daily oral antiretroviral therapy (ART) remains challenging for people with HIV due to stigma, anxiety, pill fatigue, and regimen complexity, highlighting a need for alternative treatment approaches[1,2]
- A complete ultra-long-acting (ULA) regimen is needed to offer ≥4-month dosing intervals, providing greater convenience, confidentiality, and improved tolerability while maintaining robust efficacy[1]
  - Administration frequency is a top priority among people with HIV, with dosing intervals of 4 or 6 months strongly preferred[3,4]
- N6LS is being developed to provide a highly effective treatment option as part of a future complete LA regimen that aligns with the evolving needs of people with HIV

N6LS Clinical Development

Preclinical and First-Time-in-Human

Early Data Supported N6LS Efficacy and Safety Potential

- N6LS is a broadly neutralizing antibody (bNAb) with an extended half-life[5]
  - The parental N6 antibody was isolated from an individual with broad and potent serum-neutralizing activity against HIV-1 who maintained virologic control for 21 years without ART[6]
- N6LS binds to the CD4-binding site of the HIV-1 envelope, preventing entry into the host target cell[6,7]
- N6LS showed broad neutralization and potent antiviral activity in vitro and in serum[5-7]
- In the phase 1 first-time-in-human VRC 609 study, N6LS IV (5, 20, or 40 mg/kg) or SC (5 or 20 mg/kg; ± recombinant human hyaluronidase PH20 [rHuPH20], an enzyme facilitating larger volumes and higher doses of SC agents) showed a promising pharmacokinetic (PK) and safety profile in adults without HIV[5]
  - Across all doses and administration routes, mean serum half-life was 48.6 days, and N6LS had a favorable safety profile and was well tolerated[5]

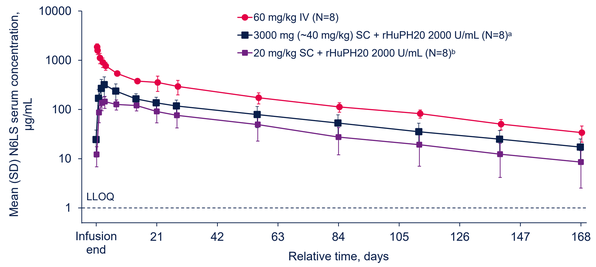
Findings from VRC 609 supported evaluation of higher N6LS doses in the phase 1 SPAN study

Phase 1: SPAN

SPAN Results Indicated N6LS Could Be Safely Administered at 60 mg/kg IV or 3000 mg SC + rHuPH20[8]

- SPAN evaluated PK, safety, and tolerability of a higher IV dose and ascending SC (+ rHuPH20) doses of N6LS in adults without HIV
- N6LS had a long terminal half-life (the median ranged from 43 to 47 days), consistent with findings from VRC 609[4]
- N6LS serum concentrations declined slowly (Figure 1)

Figure 1. N6LS Serum Concentrations After Single-Dose Administration[8]



[a]Data available for 7/8 participants on Days 21, 56, 112, 140, and 168. [b]Included values imputed as 0 for being below LLOQ (1.00 µg/mL; n=1 value each for Days 56, 84, 112, and 140 and n=2 values for Day 168).

- N6LS had a favorable safety profile

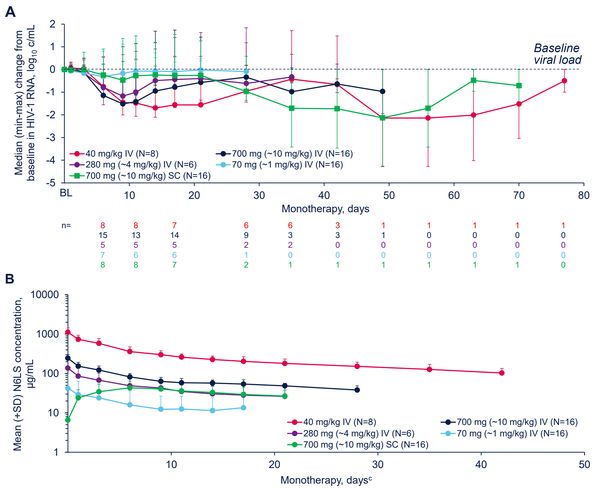
N6LS exposure-dependent antiviral activity was established across a range of doses in the proof-of-concept BANNER study

Phase 2a: BANNER

N6LS Monotherapy Showed Robust Antiviral Activity in People Naive to ART in BANNER[9]

- The randomized proof-of-concept BANNER study investigated antiviral activity, safety, and PK of a single dose of N6LS monotherapy for up to 84 days in adults with HIV-1 naive to ART
- N6LS 40 mg/kg IV and 700 mg SC were highly potent, achieving a mean maximum viral load reduction of 2.1 $\log_{10}$ c/mL (Figure 2)
- Virologic response was exposure-dependent, with higher N6LS exposures resulting in greater and longer-term viral load reductions
- Most participants who received higher N6LS IV doses achieved virologic response (viral load reduction ≥0.5 $\log_{10}$ c/mL from baseline):
  - 40 mg/kg IV, 8/8 (100%); 700 mg IV, 14/15 (93%); 280 mg IV, 5/6 (83%)
- Baseline viral sensitivity to N6LS was an important predictor of N6LS concentrations needed to achieve antiviral activity[10]

Figure 2. (A) Median Change From Baseline in Viral Load During Monotherapy[a] Up Through Day 84[b] and (B) Mean N6LS Serum Concentration Over Nominal Time (Semi-Logarithmic)[9]



[a]Monotherapy phase duration based on pre-specified criteria: virologic non-response and rebound, missing data, and reaching Day 84. [b]Mean monotherapy duration was 30.7 days. [c]For all groups, data presented for time points at which ≥3 participants had data available.

- A single dose of N6LS had a good safety profile and was well tolerated: no AEs led to study discontinuation, and no serious AEs occurred during monotherapy; all drug-related AEs were grade 1 or 2
  - 9 infusion site reactions (ISRs) were reported in 7/62 (11%) participants; all were mild in severity and resolved within a median of 4 days
  - 4/46 (9%) participants receiving N6LS IV had an ISR vs 3/16 (19%) receiving N6LS SC

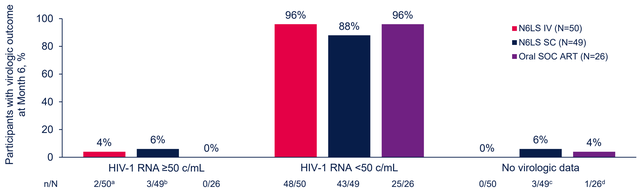
Findings from BANNER and SPAN informed dose selection for the phase 2b EMBRACE study evaluating N6LS as a partner agent in a complete LA INSTI-based regimen

Phase 2b: EMBRACE

Virologic Suppression at 6 Months Was Maintained in Participants With Baseline N6LS Sensitivity in EMBRACE

- Part 1 of EMBRACE evaluated efficacy, safety, and tolerability of every-4-month (Q4M) N6LS + monthly CAB LA as a complete LA regimen in adults with HIV-1 and virologic suppression
  - Participants received N6LS 60 mg/kg IV Q4M (N6LS IV) or N6LS 3000 mg + rHuPH20 SC Q4M (N6LS SC), each with CAB LA, or continued oral standard-of-care ART
- Participants with baseline sensitivity (90% inhibitory concentration ≤2.0 µg/mL and maximum percent inhibition >98%) receiving N6LS IV or SC + CAB LA maintained high rates of virologic suppression at 6 months (Figure 3)

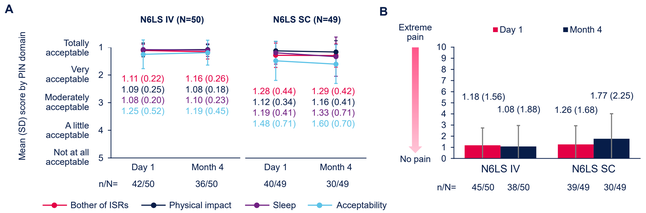
Figure 3. Snapshot Virologic Outcomes at Month 6 (Full Analysis Set)



SOC, standard of care. Participants had baseline phenotypic sensitivity to N6LS (90% inhibitory concentration ≤2.0 µg/mL and maximum percent inhibition >98%). [a]n=1 data in window not below threshold; n=1 discontinued for lack of efficacy. [b]n=1 data in window not below threshold; n=2 discontinued for lack of efficacy. [c]n=2 discontinued due to AE; n=1 discontinued for other reasons (participant withdrawal). [d]n=1 discontinued for other reasons (participant withdrawal).

- N6LS had a favorable safety, tolerability, and acceptability profile through 6 months
  - No participants in the IV group had any N6LS/CAB-related grade 3 or 4 AEs, and 8/49 (16%) in the SC group had an N6LS/CAB-related grade 3 AE, with no grade 4 AEs
  - Drug-related AEs leading to treatment discontinuation were rare (N6LS IV, 0/50; N6LS SC, 2/49), and no drug-related serious AEs were reported
  - The tolerability profile favored IV over SC administration
- Few participants had treatment-emergent anti-drug antibodies (N6LS IV, 6% [3/50]; N6LS SC, 18% [9/49])
- At Day 1 and Month 4, participants in both N6LS groups rated treatment administration as "very" or "totally" acceptable (Figure 4A)
- Both groups also reported very little pain after N6LS administration at Day 1 and Month 4 (Figure 4B)

Figure 4. Mean (SD) (A) PIN Scores by Domain and (B) NRS Scores by Treatment Group at Day 1 and Month 4



NRS, numeric rating scale; PIN, Perception of Injection.

Findings from part 1 of EMBRACE support progression to twice-yearly N6LS IV in combination with CAB LA Q2M in part 2

Conclusions

- Clinical data support N6LS IV as a robust, well-tolerated, and highly acceptable LA option for HIV-1 treatment
- N6LS showed exposure-dependent antiviral activity as monotherapy and maintained virologic suppression as a partner agent in a complete LA regimen
- Further clinical evaluation is ongoing to assess N6LS as a partner biologic in the first complete ULA 2-drug regimen paired with an INSTI

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