High-Dose VH3810109 (N6LS) ± Recombinant Human Hyaluronidase PH20: Phase 1 SPAN Study Safety Results

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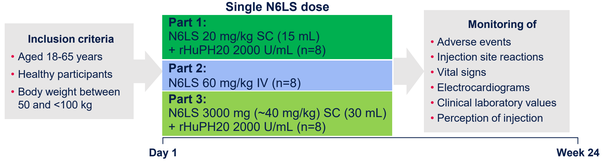
Introduction

- Broadly neutralizing antibodies are being developed for long-acting HIV-1 therapy
- VH3810109 (N6LS) is a CD4-binding site antibody with broad and potent neutralization activity in vitro that demonstrated robust antiviral effect in adults with HIV-1 in the 2-part phase 2a BANNER study
  - In BANNER part 1, N6LS led to virologic response in 93% of participants who received a single dose of either 40 mg/kg or 280 mg (~4 mg/kg) intravenously (IV)[1]
  - Few drug-related adverse events (AEs) and no serious AEs were reported with N6LS administration in BANNER[1,2]
- Administering N6LS with rHuPH20 allows for delivery of larger SC volumes and higher doses without impacting pharmacokinetics or N6LS neutralization activity[3,4]
- Here, we report safety and tolerability data from the SPAN study, which evaluated the highest single N6LS doses ever administered SC (20 mg/kg [15 mL], 3000 mg [~40 mg/kg; 30 mL] + rHuPH20) or IV (60 mg/kg)
- These results inform the dosing for the ongoing clinical development of N6LS 3000 mg SC + rHuPH20 and N6LS 60 mg/kg IV into phase 2b (EMBRACE, NCT05996471)

Methods

- SPAN is a phase 1, open-label, 3-part, 24-week trial (NCT05291520) evaluating single-dose N6LS administered IV or SC + rHuPH20 in healthy adults (Figure 1)
  - Doses were based on clinical trial data for the CD4-binding site antibody VRC01, administered IV at 5 to 40 mg/kg and SC at 5 mg/kg,[5] and for N6LS, administered IV at 40 mg/kg in part 1 of the BANNER study[1]; both antibodies were generally safe and well tolerated
  - In modeling studies based on data from BANNER parts 1 and 2, N6LS demonstrated antiviral activity at all doses (IV: ~1, ~4, ~10, and 40 mg/kg; SC: ~10 mg/kg), which correlated with N6LS exposure levels[6]
- Primary endpoints included number and proportion of participants experiencing AEs (grade ≥2) and serious AEs, and incidence of elevated liver parameters (grade ≥2) through Week 24
  - For parts 1 and 3, number and proportion of participants experiencing injection site reactions (ISRs) within 7 days of SC administration were additional primary endpoints
  - In part 2 (60 mg/kg IV), a sequential sentinel dosing strategy was employed for risk mitigation
- A secondary endpoint to assess participant perceptions of SC injections was evaluated on Days 2 and 7 post-dose using the Perception of Injection Questionnaire[7] with 5-option scales: extremely/totally, very, moderately, a little, or not at all

Figure 1. SPAN Study Design



Results

Participants

- Of the 24 total participants enrolled across the 3 study parts, mean age ranged from 39.9 to 42.8 years and 15 (63%) were female; 12 (50%) identified as White, 7 (29%) as Black or African American, and 8 (33%) as Hispanic or Latin American (Table 1)

Overall Safety Summary

- No AEs led to withdrawal and no serious AEs or deaths occurred in any dosing group
- No relevant differences in overall AE incidences were observed among the SC N6LS + rHuPH20 dose groups (Table 2)
- A higher frequency of AEs was reported with SC administration relative to IV, mainly driven by ISRs
- No clinically significant safety trends in vital signs, electrocardiograms, or laboratory values were observed

High-dose broadly neutralizing antibody VH3810109 (N6LS) was generally safe and well tolerated when administered either intravenously or subcutaneously with recombinant human hyaluronidase PH20 (rHuPH20) in healthy participants

Table 1. Participant Demographics and Baseline Characteristics

Parameter	Part 1 N6LS 20 mg/kg SC + rHuPH20 2000 U/mL (N=8)	Part 2 N6LS 60 mg/kg IV (N=8)	Part 3 N6LS 3000 mg (~40 mg/kg) SC + rHuPH20 2000 U/mL (N=8)
Age, mean (SD), y	42.8 (7.8)	40.0 (14.5)	39.9 (10.6)
Male sex, n (%)	3 (38)	1 (13)	5 (63)
Race, n (%)			
Asian	2 (25)	1 (13)	1 (13)
Black or African American	1 (13)	2 (25)	4 (50)
Multiple races	0	1 (13)	0
White	5 (63)	4 (50)	3 (38)
Hispanic or Latin American, n (%)	2 (25)	4 (50)	2 (25)
BMI, mean (SD), kg/m^2	25.2 (3.5)	28.0 (3.5)	29.2 (4.8)

Table 2. Summary of AEs Across All Doses

Participants, n (%)	Part 1 N6LS 20 mg/kg SC + rHuPH20 2000 U/mL (N=8)	Part 2 N6LS 60 mg/kg IV (N=8)	Part 3 N6LS 3000 mg (~40 mg/kg) SC + rHuPH20 2000 U/mL (N=8)	Total (N=24)
Any AE	8 (100)	1 (13)	8 (100)	17 (71)
Grade 3 AEs (all injection site erythema)	6 (75)	0	8 (100)	14 (58)
Grade 4 AEs	0	0	0	0
Serious AEs	0	0	0	0
Drug-related AEs	7 (88)	0	8 (100)	15 (63)
Grade ≥3 drug-related AEs (all ISRs)	6 (75)	0	8 (100)	14 (58)
AEs leading to withdrawal	0	0	0	0
Deaths	0	0	0	0
AEs occurring in >1 participant by preferred term and study part				
Injection site bruising	0	0	2 (25)	2 (8)
Injection site erythema	7 (88)	0	8 (100)	15 (63)
Injection site pain	1 (13)	0	2 (25)	3 (13)
Muscle tightness	1 (13)	1 (13)	0	2 (8)
Nasopharyngitis	0	0	2 (25)	2 (8)
Upper respiratory tract infection	2 (25)	0	1 (13)	3 (13)
Viral infection	1 (13)	0	1 (13)	2 (8)

Note: At each level of summarization, a participant was counted once if the participant reported 1 or more events; therefore, the sum of AEs may be greater than reported at each level of summarization.

ISRs

- No ISRs were reported in part 2 (IV administration)
- In parts 1 and 3 (SC administration), 32 ISRs were reported by 15/16 (94%) participants (Table 3)
  - All grade 3 ISRs were injection site erythema, with a mean duration of 2.9 days (part 1) and 5.7 days (part 3; Figure 2)
  - No local secondary infections or abscesses were reported with ISRs
- All ISRs resolved without sequelae or treatment
- The majority of ISRs resolved within 7 days; only 1 ISR had a longer time to resolution (part 3, 27 days)
- Biphasic injection site erythema was reported in parts 1 (2/8 [25%]) and 3 (4/8 [50%])

Table 3. Summary of ISRs Across All Doses

Participants, n (%)	Part 1 N6LS 20 mg/kg SC + rHuPH20 2000 U/mL (N=8)	Part 2 N6LS 60 mg/kg IV (N=8)	Part 3 N6LS 3000 mg (~40 mg/kg) SC + rHuPH20 2000 U/mL (N=8)	Total (N=24)
ISRs (all within 7 days of administration)	7 (88)	0	8 (100)	15 (63)
Grade 1	2 (25)	0	3 (38)	5 (21)
Injection site bruising	0	0	2 (25)	2 (8)
Injection site induration	0	0	1 (13)	1 (4)
Injection site pain	1 (13)	0	2 (25)	3 (13)
Injection site pruritus	1 (13)	0	0	1 (4)
Injection site warmth	0	0	1 (13)	1 (4)
Grade 2	2 (25)	0	2 (25)	4 (17)
Injection site erythema	2 (25)	0	2 (25)	4 (17)
Injection site pruritus	1 (13)	0	0	1 (4)
Grade 3	6 (75)	0	8 (100)	14 (58)
Injection site erythema	6 (75)	0	8 (100)	14 (58)
Grade ≥4	0	0	0	0
Number of ISR events	14	0	18	32

Note: At each level of summarization, a participant was counted once if the participant reported 1 or more events; therefore, the sum of ISRs may be greater than reported at each level of summarization.
[a]All grade 3 ISRs were injection site erythema based on size with no reports of complications (eg, secondary infection, ulceration, phlebitis, sterile abscess, drainage, or symptoms causing inability to perform usual social and functional activities).

Figure 2. Grade 3 Injection Site Erythema With the Largest Surface Areas[a] Among Participants in Part 3

[a]In part 3, 3/8 (38%) participants experienced grade 3 injection site erythema with larger measurements compared with others in the group. In these 3 participants, peak measurement for injection site erythema was reached on Day 3 or 4, with large reductions in surface area the day after peak surface area was reached. ISRs were well tolerated and resolved without sequelae or treatment, with all participants denying any considerable pain, tenderness, or discomfort throughout.

Perception of Injection Questionnaire (SC Dosing)

- In the N6LS 20 mg/kg SC group, no participants reported being affected by local reactions or pain when falling asleep, changing position at night, moving, or walking on Days 2 and 7 post-dose
- In the N6LS 3000 mg (~40 mg/kg) group, most (75%-100% per question) participants felt "not at all" affected by local reactions or pain
  - On Day 2 post-dose, 1 participant was affected by local reactions when falling asleep "a little"; 3 participants were affected by local reactions when changing positions at night ("a little," n=1; "moderately," n=1) or pain ("a little," n=1)
  - On Day 7 post-dose, 2 participants were affected by local reactions when falling asleep, 2 were affected by pain when changing positions at night, and 1 was affected by local reactions and pain when moving or walking ("a little" for each)
- Participants receiving SC injections found local reactions and pain acceptable at both Day 2 and Day 7 (Figures 3 and 4)

Figure 3. Perception of Injection Questionnaire Responses From Participants Receiving N6LS 20 mg/kg SC + rHuPH20 (N=8)

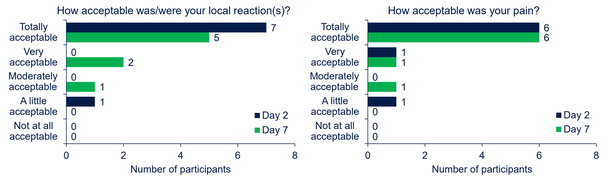
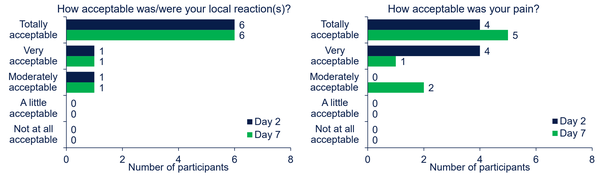


Figure 4. Perception of Injection Questionnaire Responses From Participants Receiving N6LS 3000 mg (~40 mg/kg) SC + rHuPH20 (N=8)



Conclusions

- High-dose N6LS administered IV (60 mg/kg) or SC (20 mg/kg in 15 mL or ~40 mg/kg in 30 mL) + rHuPH20 was generally safe and well tolerated in this study
- Across doses, there were no serious AEs or deaths; no AEs that led to withdrawal; and no clinically significant changes from baseline in vital signs, electrocardiograms, or laboratory values
- A higher frequency of AEs was reported with SC administration compared with IV, mainly driven by ISRs
  - All grade 3 AEs were injection site erythema that resolved without sequelae or treatment after a mean duration ranging from 2.9 to 5.7 days
- All participants rated local reactions and pain as acceptable
- Results from SPAN support the dose selection and ongoing clinical development of N6LS 60 mg/kg IV and N6LS 3000 mg (~40 mg/kg) SC + rHuPH20 into phase 2b (EMBRACE, NCT05996471)
- Additional data on the efficacy of N6LS administered at lower doses (70 mg [~1 mg/kg], 280 mg [~4 mg/kg], and 700 mg [~10 mg/kg] and 40 mg/kg IV or 700 mg [~10 mg/kg] SC) in people living with HIV-1 from the BANNER study are presented in Oral Presentation 117[8]

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