Cutoff for Baseline Phenotypic Sensitivity to VH3810109 (N6LS) Did Not Impact Occurrence of Confirmed Virologic Failure in the Phase 2b EMBRACE Study

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Key Takeaways

- **In the phase 2b EMBRACE study, 72% of individuals with proviral VH3810109 (N6LS) sensitivity results at screening met inclusion criteria for the study**
- **Occurrence of confirmed virologic failure (n=4) was not attributed to the phenotypic sensitivity cutoff or N6LS exposures**
- **No significant associations between baseline characteristics and N6LS phenotypic sensitivity were observed**

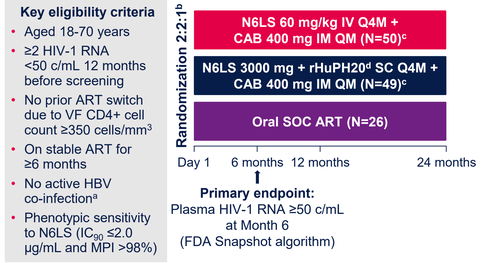
Purpose

- VH3810109 (N6LS) is a broadly neutralizing CD4-binding site antibody in development for ultra-long-acting HIV-1 treatment[1-3]
- In part 1 of the EMBRACE study, N6LS administered intravenously (IV) or subcutaneously (SC) with recombinant human hyaluronidase PH20 (rHuPH20) every 4 months (Q4M) + monthly intramuscular long-acting cabotegravir (CAB LA) demonstrated a favorable safety and tolerability profile and maintained viral suppression in a high proportion of adults with baseline N6LS sensitivity (IV, 96%; SC, 88%)[3]
- Here, we evaluate the impact of baseline proviral phenotypic N6LS sensitivity and N6LS exposures on confirmed virologic failure (CVF) through 6 months in EMBRACE

Methods

- EMBRACE is a randomized, open-label, multicenter, phase 2b study in adults with screening HIV-1 RNA <50 c/mL and proviral phenotypic sensitivity to N6LS (IC_{90} ≤2.0 µg/mL and maximum percent inhibition [MPI] >98%; Figure 1)
  - Proviral phenotypic sensitivity to N6LS was determined using the PhenoSense® mAb DNA assay (Monogram Biosciences, South San Francisco, CA) using peripheral blood mononuclear cell (PBMC) samples from screening

Figure 1. Part 1 Study Design



ART, antiretroviral therapy; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IM, intramuscular; QM, monthly; 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).

- CVF was defined as 2 consecutive HIV-1 RNA values ≥200 c/mL
  - We used the cobas® HIV-1 6800 assay (Roche, Basel, Switzerland) for HIV-1 RNA quantitation
  - Potential on-treatment resistance was determined using the appropriate PhenoSense GT assay and/or the PhenoSense mAb RNA assay using plasma samples collected at suspected virologic failure (SVF; first HIV-1 RNA ≥200 c/mL) and/or CVF
  - Potential causes for CVF beyond new immunizations, intercurrent illness, or adverse events were not evaluated

Results

- 125 participants were randomized and received ≥1 dose of study treatment in EMBRACE
- Demographics and baseline characteristics were well balanced among treatment groups (Table 1)

Table 1. Participant Demographics and Baseline Characteristics

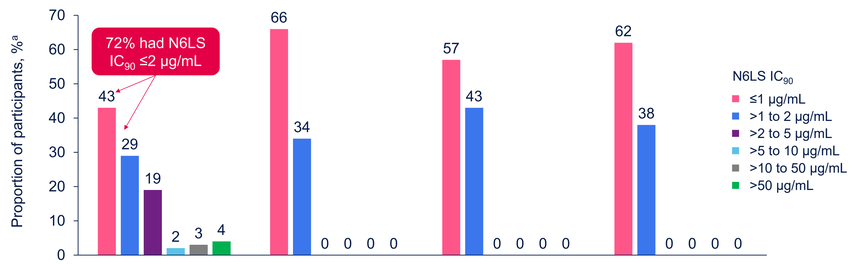
Parameter	N6LS 60 mg/kg IV (N=50)	N6LS 3000 mg + rHuPH20 SC (N=49)	Oral SOC ART (N=26)[a]	Total (N=125)
Age, median (range), y	53 (28-69)	53 (22-67)	47 (25-68)	53 (22-69)
Male, n (%)[b]	44 (88)	39 (80)	21 (81)	104 (83)
Race, n (%)				
Asian	0	2 (4)	1 (4)	3 (2)
Black or African American	11 (22)	19 (39)	5 (19)	35 (28)
White	37 (74)	26 (53)	16 (62)	79 (63)
Other races/Missing[c]	2 (4)	2 (4)	4 (15)	8 (6)
Ethnicity, Hispanic or Latin American, n (%)	18 (36)	21 (43)	15 (58)	54 (43)
CD4+ cell count, median (range), cells/mm³	602 (309-1210)	759 (351-1635)	644 (307-1174)	647 (307-1635)
N6LS IC_{90}, median (range), µg/mL[d]	0.76 (0.21-1.92)	0.85 (0.12-1.97)	0.94 (0.24-1.96)	0.83 (0.12-1.97)

INSTI, integrase strand transfer inhibitor. [a]88% (23/26) of participants in the oral SOC ART group were using INSTI-based regimens. [b]Sex assigned at birth. [c]Included American Indian or Alaska Native (n=2), individuals of multiple races (n=1), and not reported or unknown (n=5). [d]Phenotypic sensitivity measured using PBMC-derived proviral DNA. All participants were sensitive to N6LS (IC_{90} ≤2.0 µg/mL) per inclusion criteria.

Proviral DNA Phenotypic Susceptibility to N6LS at Screening

- Among adults with viral suppression who were screened for inclusion in EMBRACE, proviral DNA N6LS IC_{90} values varied broadly, from 0.12 to >50 µg/mL (Figure 2)
  - 72% (182/253) of screened participants with available phenotypic results had IC_{90} ≤2 µg/mL and MPI >98%, meeting inclusion criteria
- Proportions with baseline IC_{90} ≤1 vs >1 to 2 µg/mL were similar across groups (Figure 2)

Figure 2. Proviral DNA Phenotypic Susceptibility to N6LS at Screening



N6LS IC_{90}, µg/mL	Screened (N=253)	N6LS 60 mg/kg IV (N=50)	N6LS 3000 mg + rHuPH20 SC (N=49)	Oral SOC ART (N=26)
Median (range)	1.22 (0.12-50.00)	0.76 (0.21-1.92)	0.85 (0.12-1.97)	0.94 (0.24-1.96)
GM (CV%)	1.43 (171.08)	0.79 (51.15)	0.81 (68.80)	0.88 (54.86)
Participants with subsequent CVF	NA	n=2; 0.60 and 1.26	n=2; 0.80 and 0.94	n=0; NA

[a]Among screened participants with available phenotypic results.

Association Between Baseline Characteristics and Phenotypic Sensitivity

- No statistically significant association between N6LS phenotypic sensitivity and baseline characteristics such as sex, age, race, time since HIV diagnosis, CD4+ cell count, or CD4+/CD8+ ratio were observed (post hoc analysis)
  - A trend toward higher phenotypic sensitivity was noted in virus isolates from individuals who identified as Hispanic or Latin American compared with those who did not, though this did not reach statistical significance (*P*=0.0537)

CVF Through Month 6

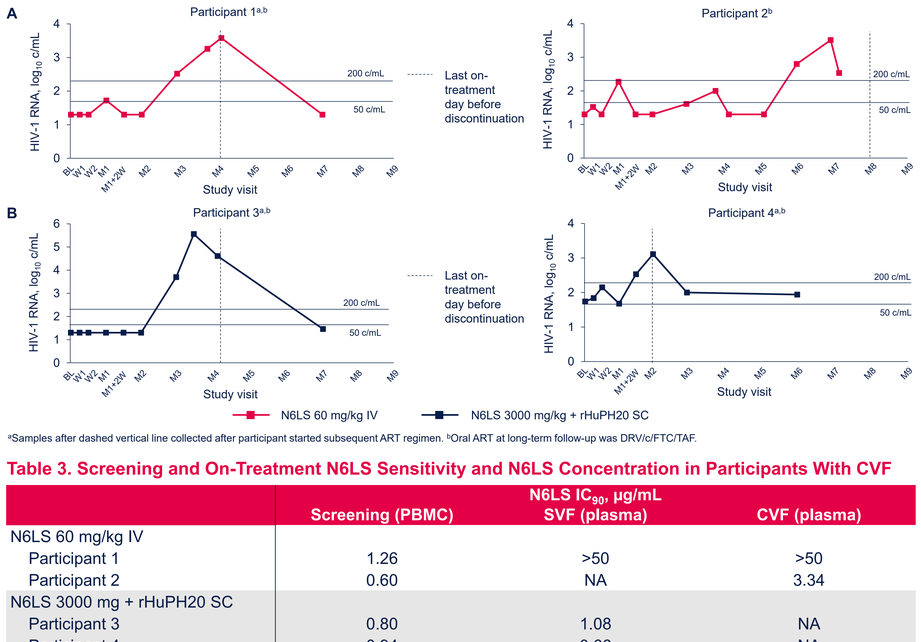
- Through Month 6, a total of 4 participants receiving N6LS (n=2 in each group) met CVF (Table 2; Figure 3)
  - Of these, 3 participants had baseline IC_{90} ≤1 µg/mL (Table 2)
- Both IV group participants showed N6LS insensitivity (IC_{90} >50 µg/mL) or reduced sensitivity (IC_{90} >2 µg/mL) at CVF (Table 3)
  - No INSTI resistance-associated mutations were detected at baseline, SVF, or CVF
- In the SC group, both participants remained sensitive to N6LS at SVF (Table 3)
  - INSTI RAM Q148R was detected in 1 participant post-CVF; however, phenotypic testing showed sensitivity to CAB (FC 2.17), BIC (FC 1.09), and DTG (FC 0.52)

Table 2. Baseline Characteristics of Participants Meeting CVF Criteria

Parameter	Participant 1	Participant 2	Participant 3	Participant 4
N6LS group	IV	IV	SC	SC
Sex	Male	Male	Male	Male
Age, y	69	32	53	44
BMI, kg/m²	22.6	26.7	28.4	30.4
Baseline CDC stage[a]	Stage 2	Stage 2	Stage 1	Stage 3
Time since HIV diagnosis, y	22	1	16	7
HIV-1 RNA, c/mL	<20	<20	<20	55[b]
CD4+ cell count, cells/mm³	528	316[c]	952	450
N6LS IC_{90}, µg/mL	1.26	0.60	0.80	0.94
HIV-1 subtype	B	B	B	B

[a]Baseline is lifetime classification collected at screening. [b]Screening HIV-1 RNA <20 c/mL per inclusion criteria. [c]Participant 2 excluded from per-protocol population due to inclusion/exclusion criteria violation: screening CD4+ cell count 318 vs ≥350 cells/mm³ required for eligibility.

Figure 3. CVF in Participants Receiving (A) N6LS 60 mg/kg IV and (B) N6LS 3000 mg + rHuPH20 SC



[a]Samples after dashed vertical line collected after participant started subsequent ART regimen. [b]Oral ART at long-term follow-up was DRV/c/FTC/TAF.

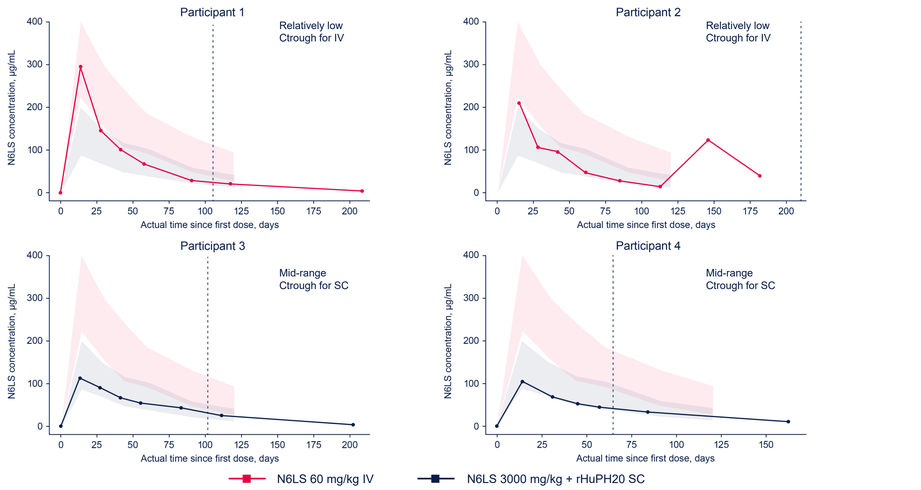
Table 3. Screening and On-Treatment N6LS Sensitivity and N6LS Concentration in Participants With CVF

	N6LS IC_{90}, µg/mL		
	Screening (PBMC)	SVF (plasma)	CVF (plasma)
N6LS 60 mg/kg IV			
Participant 1	1.26	>50	>50
Participant 2	0.60	NA	3.34
N6LS 3000 mg + rHuPH20 SC			
Participant 3	0.80	1.08	NA
Participant 4	0.94	0.66	NA

NA, not available.

- There was a trend toward lower N6LS exposures among participants with CVF (Figure 4)
- All participants with CVF had CAB Ctrough concentrations exceeding 4× PA-IC_{90} for wild-type HIV (>0.6 µg/mL)[4]
- No CVFs were attributable to factors such as immunizations or intercurrent illness

Figure 4. Individual Serum N6LS Concentrations in Participants Meeting CVF Criteria



All participants with CVF received 1 dose of N6LS before CVF. Shaded areas show minimum and maximum N6LS concentrations for responders in the IV (light pink) and SC (light blue) groups.

Conclusions

- In this virologically suppressed population screened for eligibility in EMBRACE, 72% of participants with proviral sensitivity results met inclusion criteria for N6LS phenotypic sensitivity
  - Viral suppression was maintained in 96% of the IV group and 88% of the SC group[3]
- Results from this study do not suggest an association between CVF and phenotypic sensitivity cutoff or CVF and N6LS or CAB exposures
- Identifying risk factors for CVF during treatment with N6LS-containing regimens requires further investigation, and a larger data set will be needed
- For additional data on N6LS, please see Oral presentation PS09.1 and Posters eP131 and MeP10.1[5-7]

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