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Safety and Tolerability of N6LS Administered Intravenously or Subcutaneously: Promising Results From Part 1 of the EMBRACE Study

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Disclosures

- Peter Leone is an employee of ViiV Healthcare and owns stock in GSK

Introduction

- Long-acting and ultra-long-acting (ULA) ART offers a convenient, sustainable solution 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 ULA HIV-1 treatment
- In the phase 2b EMBRACE study, we evaluated efficacy, safety, and tolerability of N6LS every 4 months + approved monthly CAB LA IM for maintenance of HIV-1 suppression[1]
  - At Month 6, N6LS administered IV or SC + rHuPH20 maintained viral suppression in a high proportion of adults with baseline N6LS sensitivity[1]
- Here, we present detailed safety data and participant-reported tolerability through 6 months in EMBRACE

ART, antiretroviral therapy; CAB, cabotegravir; IM, intramuscular; IV, intravenous; LA, long-acting; N6LS, VH3810109; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

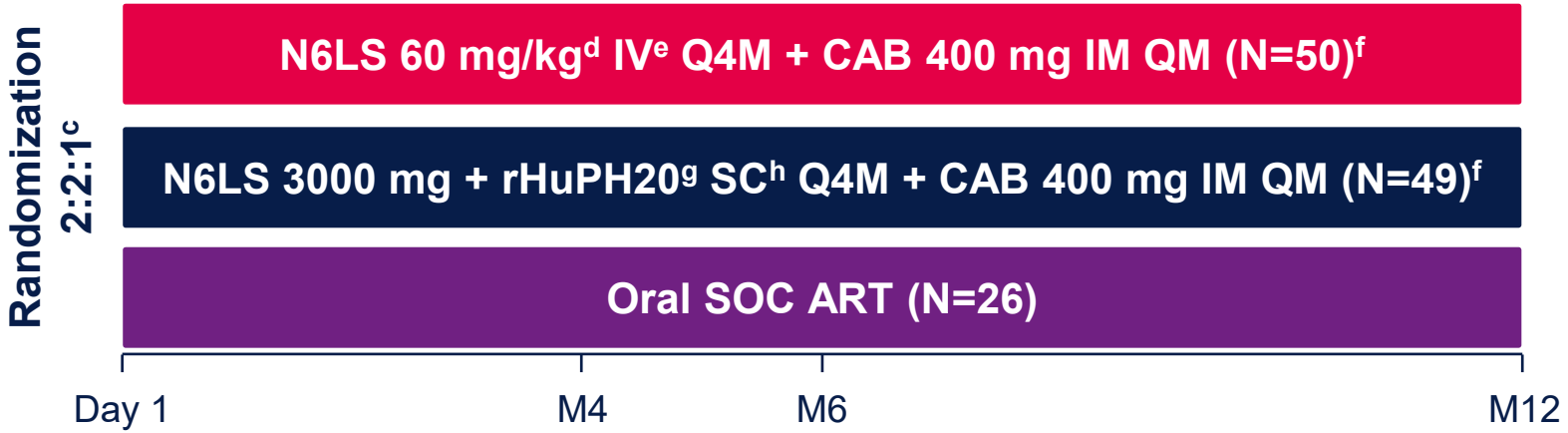
1. Taiwo et al. CROI 2025; San Francisco, CA. Oral presentation 203.

Study Design

Randomized, open-label, multicenter, phase 2b study

Key eligibility criteria

- Aged 18-70 years
- ≥2 HIV-1 RNA <50 c/mL 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%)[b]



Participant-reported tolerability was evaluated at Day 1 and Month 4

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; N6LS, VH3810109; QM, monthly; Q4M, every 4 months; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SOC, standard of care; VF, virologic failure.

[a]Individuals positive for HBsAg or negative for HBsAg but positive for HBcAb with detectable HBV DNA excluded. [b]Performed using PhenoSense® mAb DNA assay (Monogram Biosciences, South San Francisco, CA) using peripheral blood mononuclear cell samples from screening. [c]Stratified by N6LS IC_{90} > or ≤1.0 µg/mL. [d]Equating to 4200 mg for the average 70 kg individual. [e]N6LS diluted with normal saline to infuse ~250 mL of solution at appropriate concentration over ~60 min. [f]CAB 600 mg IM loading dose on Day 1. [g]rHuPH20 sourced from Halozyme Therapeutics, Inc (San Diego, CA). [h]N6LS mixed with rHuPH20 in the pharmacy and administered via standard Medfusion® 3500 (Smiths Medical, St Paul, MN) syringe pump (or equivalent) in 1 infusion site at a rate of ≤3 mL/min.

Demographics and Baseline Characteristics Were Well Balanced Across Groups

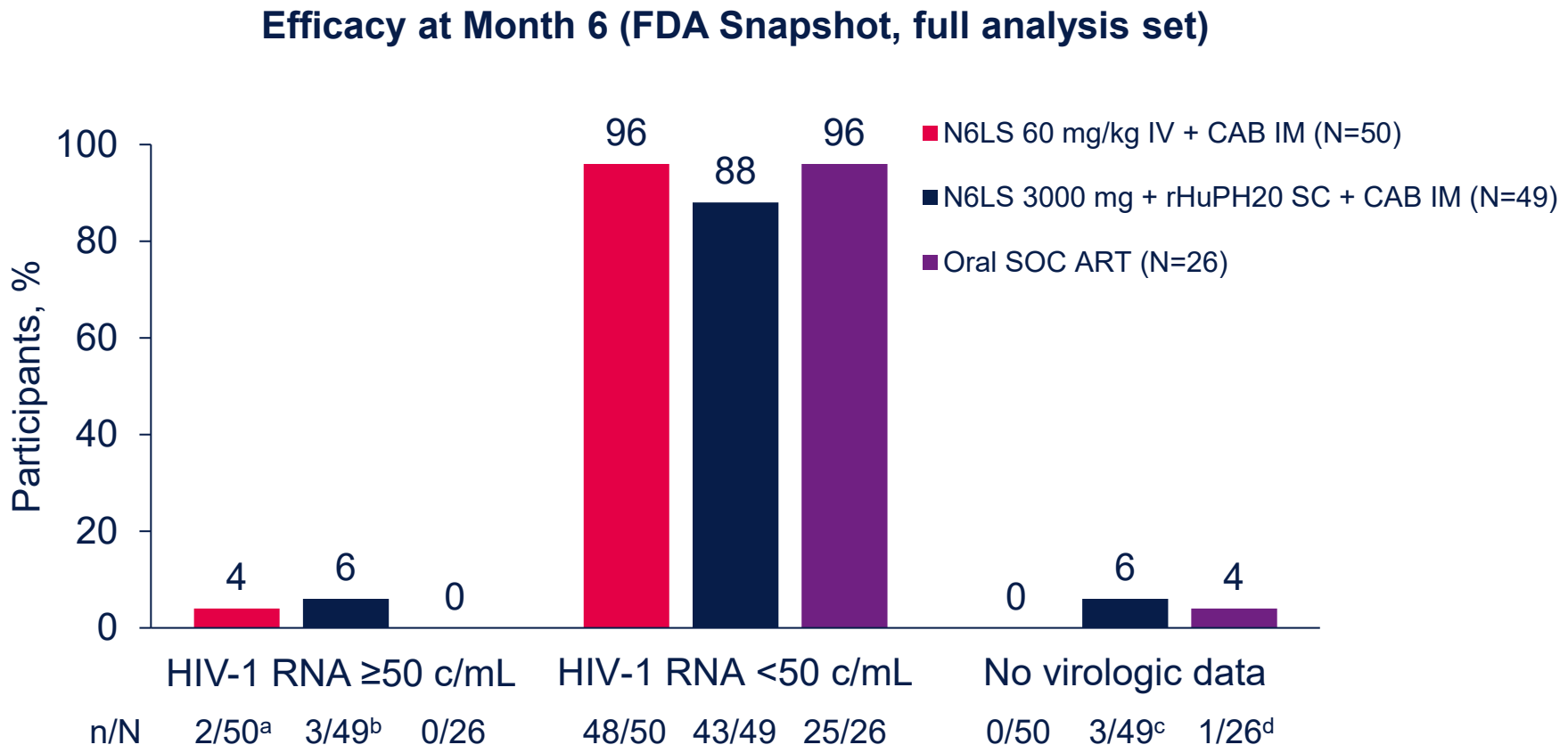
Parameter	N6LS 60 mg/kg IV + CAB IM (N=50)	N6LS 3000 mg + rHuPH20 SC + CAB IM (N=49)	Oral SOC ART (N=26)[a]	Total (N=125)
Age, median (range), y	53 (28-69)	53 (22-67)	47 (25-68)	53 (22-69)
Male, n (%)[b]	44 (88)	39 (80)	21 (81)	104 (83)
Race, n (%)				
Asian	0	2 (4)	1 (4)	3 (2)
Black or African American	11 (22)	19 (39)	5 (19)	35 (28)
White	37 (74)	26 (53)	16 (62)	79 (63)
Ethnicity, Hispanic or Latin American, n (%)	18 (36)	21 (43)	15 (58)	54 (43)
Weight, median (range), kg	81 (60-109)	81 (58-112)	86 (57-136)	83 (57-136)
Body mass index, median (range), kg/m^2	27 (17-37)	27 (19-40)	29 (21-40)	28 (17-40)
CD4+ cell count, median (range), cells/mm^3	602 (309-1210)	759 (351-1635)	644 (307-1174)	647 (307-1635)
N6LS IC_{90} phenotypic sensitivity[c]				
Median (range), µg/mL	0.76 (0.21-1.92)	0.85 (0.12-1.97)	0.94 (0.24-1.96)	0.83 (0.12-1.97)
≤1 µg/mL, n (%)	33 (66)	28 (57)	16 (62)	77 (62)
>1 to ≤2 µg/mL, n (%)	17 (34)	21 (43)	10 (38)	48 (38)

ART, antiretroviral therapy; CAB, cabotegravir; IC_{90}, 90% inhibitory concentration; IM, intramuscular; INSTI, integrase strand transfer inhibitor; IV, intravenous; N6LS, VH3810109; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SOC, standard of care.

[a]23/26 (88%) participants in the oral SOC ART group were using INSTI-based regimens. [b]Sex assigned at birth. [c]All participants were sensitive to N6LS (IC_{90} ≤2.0 µg/mL) per inclusion criteria.

Griesel et al. EACS 2025; Paris, France. Oral presentation PS09.1.

N6LS + CAB Maintained Viral Suppression in a High Proportion of Adults With Baseline N6LS Sensitivity



ART, antiretroviral therapy; CAB, cabotegravir; FDA, US Food and Drug Administration; IM, intramuscular; IV, intravenous; N6LS, VH3810109; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SOC, standard of care.

[a]n=1 data in window not below threshold and n=1 discontinued for lack of efficacy. [b]n=1 data in window not below threshold and n=2 discontinued for lack of efficacy. [c]n=2 discontinued due to adverse event and n=1 discontinued for other reasons (participant withdrawal). [d]n=1 discontinued for other reasons (participant withdrawal).

Griesel et al. EACS 2025; Paris, France. Oral presentation PS09.1.

N6LS + CAB Was Generally Well Tolerated

- N6LS was generally well tolerated when given IV, with no AEs leading to withdrawal and no N6LS- or CAB-related serious AEs reported
- **No serious or severe immune reactions**, including anaphylaxis and cytokine release syndrome, or neutropenia occurred[a]
- No clinically meaningful findings in laboratory tests were attributed to N6LS IV or SC
- CAB LA QM safety and tolerability were consistent with product label

Participants, n (%)	N6LS 60 mg/kg IV + CAB IM (N=50)	N6LS 3000 mg + rHuPH20 SC + CAB IM (N=49)	Oral SOC ART (N=26)
Any AE[b]	46 (92)	40 (82)	17 (65)
Grade 1-2	41 (82)	23 (47)	15 (58)
Grade 3	5 (10)	15 (31)	1 (4)
Grade 4	0	2 (4)	1 (4)
Any N6LS/CAB-related AE	32 (64)	32 (65)	—
Grade 3	0	8 (16)[c]	—
Grade 4	0	0	—
Any N6LS/CAB-related AE excluding ISRs	14 (28)	9 (18)	—
Occurring in ≥5% of participants			
Fatigue	6 (12)	1 (2)	—
Headache	4 (8)	1 (2)	—
Any serious AE	0	3 (6)	2 (8)
N6LS/CAB-related serious AEs	0	0	—
N6LS/CAB-related AEs leading to withdrawal	0	2 (4)[d]	0

AE, adverse event; ART, antiretroviral therapy; CAB, cabotegravir; IM, intramuscular; ISR, infusion site reaction; IV, intravenous; LA, long-acting; N6LS, VH3810109; QM, monthly; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SOC, standard of care.

[a]1 participant in the N6LS IV group and 1 in the SOC group had a shift from grade 0 to 1 in absolute neutrophil count; no shifts to grade >1 occurred. [b]AEs occurring in ≥10% of participants receiving N6LS IV included injection site pain, fatigue, COVID-19, increased lipase, and headache. AEs occurring in ≥10% of participants receiving N6LS SC included infusion site erythema, injection site pain, infusion site pain, infusion site induration, infusion site swelling, and injection site nodule. [c]Included infusion site erythema (n=6), infusion site swelling (n=3), infusion site induration (n=2), and CAB-related injection site pain (n=1). [d]Included CAB-related grade 3 injection site pain (n=1) and grade 2 anxiety and depression related to N6LS and CAB in a participant with history of depression (n=1).

Griesel et al. EACS 2025; Paris, France. Oral presentation PS09.1.

Fewer ISRs and Better Tolerability With IV Administration of N6LS[a]

Parameter	N6LS 60 mg/kg IV + CAB IM (N=50)	N6LS 3000 mg + rHuPH20 SC + CAB IM (N=49)
Participants reporting any ISR, n (%)	4 (8)	25 (51)
Number of ISR events, n[b]	4	70
Grade ≥3, n (%)	0	11 (16)
ISR duration, median (range), days	2 (1-3)	4 (1-14)
ISR duration, n (%)		
1-7 days	4 (100)	42 (60)
8-14 days	0	27 (39)[c]
ISRs leading to discontinuation	0	0

- 4 ISRs (all grade 1) were reported in the N6LS IV group; all resolved within 3 days
- 25 participants in the SC group experienced 70 ISRs (all grade 1-3); all resolved within 14 days

CAB, cabotegravir; IM, intramuscular; ISR, infusion site reaction; IV, intravenous; N6LS, VH3810109; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

[a]Results based on data collected until last participant completed Month 6, including available on-treatment data for participants continuing study intervention beyond Month 6. [b]Total number of N6LS infusions: IV, n=125; SC, n=119. [c]n=1 missing.

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N6LS-Related ISRs Were Rare With IV Administration

	N6LS 60 mg/kg IV + CAB IM (N=50)				N6LS 3000 mg + rHuPH20 SC + CAB IM (N=49)			
	Maximum grade				Maximum grade			
Participants, n (%)	**1**	**2**	**3**	**Total**	**1**	**2**	**3**	**Total**
Erythema	1 (2)	0	0	1 (2)	7 (14)	4 (8)	6 (12)	17 (35)
Pain	2 (4)	0	0	2 (4)	7 (14)	3 (6)	0	10 (20)
Swelling	1 (2)	0	0	1 (2)	2 (4)	2 (4)	3 (6)	7 (14)
Induration	0	0	0	0	0	4 (8)	2 (4)	6 (12)
Pruritus	0	0	0	0	4 (8)	0	0	4 (8)
Bruising	0	0	0	0	3 (6)	0	0	3 (6)
Discoloration	0	0	0	0	1 (2)	0	0	1 (2)
Hematoma	0	0	0	0	1 (2)	0	0	1 (2)
Nodule	0	0	0	0	1 (2)	0	0	1 (2)
Reaction	0	0	0	0	1 (2)	0	0	1 (2)
Warmth	0	0	0	0	1 (2)	0	0	1 (2)

CAB, cabotegravir; IM, intramuscular; ISR, infusion site reaction; IV, intravenous; N6LS, VH3810109; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

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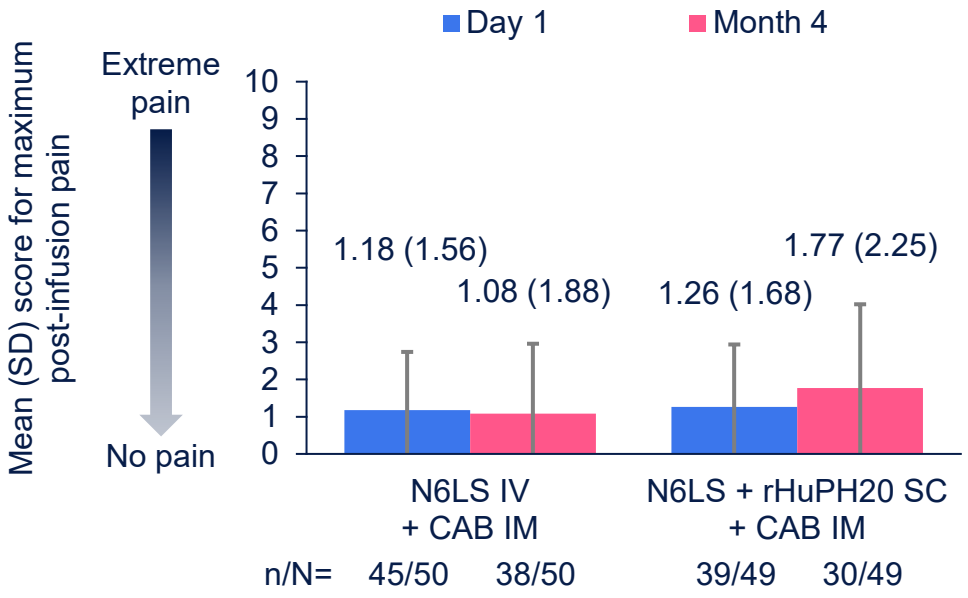
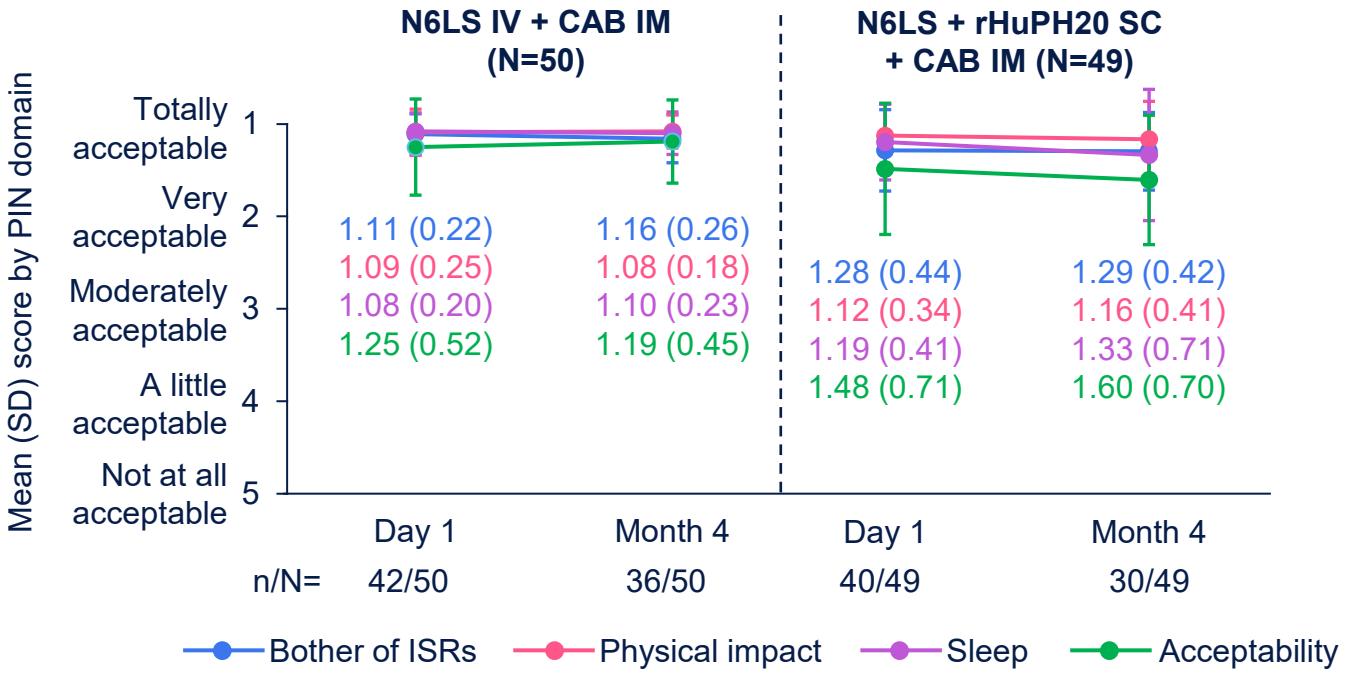
Participants Reported Low Pain and High Tolerability of N6LS + CAB Regimens

NRS (pain) scores by treatment group



PIN (tolerability) scores by domain



- Findings were sustained from Day 1 to Month 4

CAB, cabotegravir; IM, intramuscular; ISR, infusion site reaction; IV, intravenous; N6LS, VH3810109; NRS, numeric rating scale; PIN, Perception of Injection; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

Griesel et al. EACS 2025; Paris, France. Oral presentation PS09.1.

Conclusions

- N6LS every 4 months + monthly CAB demonstrated a favorable safety profile
  - N6LS IV and SC had a generally similar safety profile to other ULA small-molecule ART[1]
- Participants deemed both N6LS + CAB regimens highly tolerable
- IV administration of N6LS demonstrated a better tolerability profile vs SC
- Based on efficacy, safety, and the positive participant experience, twice-yearly N6LS IV in combination with CAB LA every 2 months is being evaluated in part 2 of the EMBRACE study

For additional data on N6LS, please see Posters eP127, eP131, and MeP10.1[2-4]

ART, antiretroviral therapy; CAB, cabotegravir; IV, intravenous; LA, long-acting; N6LS, VH3810109; SC, subcutaneous; ULA, ultra-long-acting.

1. Ogbuagu et al. CROI 2025; San Francisco, CA. Oral presentation 151. **2.** Gartland et al. EACS 2025; Paris, France. Poster eP127. **3.** Gutner et al. EACS 2025; Paris, France. Poster eP131. **4.** Edwards et al. EACS 2025; Paris, France. Poster MeP10.1.

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As the only pharmaceutical company solely focused on HIV, ViiV Healthcare's mission to leave no person living with HIV behind is resolute. We have an unwavering commitment to developing innovative medicines for the treatment and prevention of HIV in impacted communities. Clinical trial enrollment and real-world evidence generation that is representative of the populations most impacted by HIV is essential to delivering on our mission.

Plain Language Summary

Why did you conduct this study?

- N6LS is a type of antibody that can recognize and stop HIV from infecting healthy cells
- N6LS could help keep HIV under control for longer periods when combined with another HIV medicine, cabotegravir (CAB)
- We conducted this study to see how effective and safe these treatments are together and how people feel about getting them (like pain or side effects). This presentation focused on safety and how people felt about getting the medicines

What did you find?

- Most people who got N6LS (either by IV or under the skin) plus CAB kept their HIV under control for at least 6 months
- Most side effects were mild, with few serious reactions. Getting N6LS by IV was more comfortable and caused fewer skin problems than getting it under the skin
- Participants said the treatments were easy to tolerate and didn’t cause much pain

Why is this important?

- If HIV can be treated with a medicine like N6LS just a few times a year, it could make life easier for people living with HIV, help them stick to their treatment, and bring hope for even better treatments in the future
- Based on these results, we have decided to study N6LS given IV every 6 months in combination with CAB

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