Maintenance of HIV Suppression at 12 Months With Lotivibart (VH3810109, N6LS) Q4M + CAB LA QM: The EMBRACE Study

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Introduction

- LA and ULA (≥Q4M) injectable ART can improve adherence and virologic suppression, enhance quality of life, and strengthen public health impact by expanding treatment options
- Lotivibart (LVB; VH3810109, N6LS) is a broadly neutralizing CD4-binding site antibody in development for ULA HIV-1 treatment
- Part 1 of the EMBRACE study evaluated efficacy, safety, and tolerability of LVB Q4M + monthly intramuscular CAB LA to maintain HIV-1 suppression
  - At Month 6, LVB IV and SC maintained virologic suppression in 96% and 88% of participants with baseline LVB sensitivity, respectively; IV showed more favorable safety and tolerability
- Here, we present 12-month efficacy, safety, tolerability, and participant-reported outcome results from a planned interim analysis of EMBRACE part 1

ART, antiretroviral therapy; CAB, cabotegravir; IV, intravenous; LA, long-acting; LVB, lotivibart; Q4M, every 4 months; SC, subcutaneous; ULA, ultra-long-acting.

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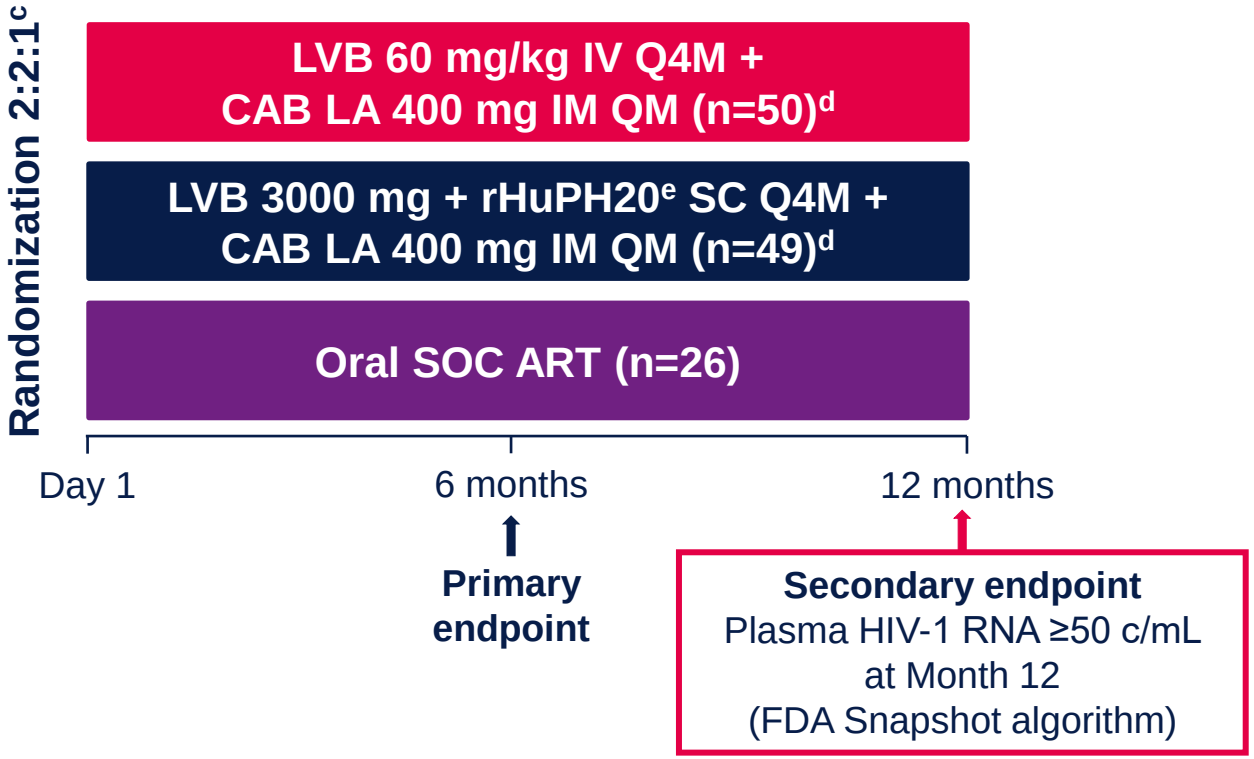
Study Design

Randomized, open-label, multicenter, phase 2b study conducted at 45 sites in the United States and Puerto Rico

Key inclusion/exclusion criteria

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



ART, antiretroviral therapy; CAB, cabotegravir; FDA, US Food and Drug Administration; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IC_{90}, 90% inhibitory concentration; IM, intramuscular; IV, intravenous; LA, long-acting; LVB, lotivibart; mAb, monoclonal antibody; MPI, maximum percent inhibition; PBMC, peripheral blood mononuclear cell; QM, every month; Q4M, every 4 months; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SOC, standard of care; VF, virologic failure.

[a]Performed using the PhenoSense® mAb DNA assay (Monogram Biosciences, South San Francisco, CA) using PBMC samples obtained at screening. [b]Individuals positive for HBsAg or negative for HBsAg but positive for HBcAb with detectable HBV DNA were excluded. [c]Stratified by LVB IC_{90} > or ≤1.0 µg/mL. [d]CAB 600 mg IM loading dose on Day 1. [e]rHuPH20 sourced from Halozyme Therapeutics, Inc (San Diego, CA).

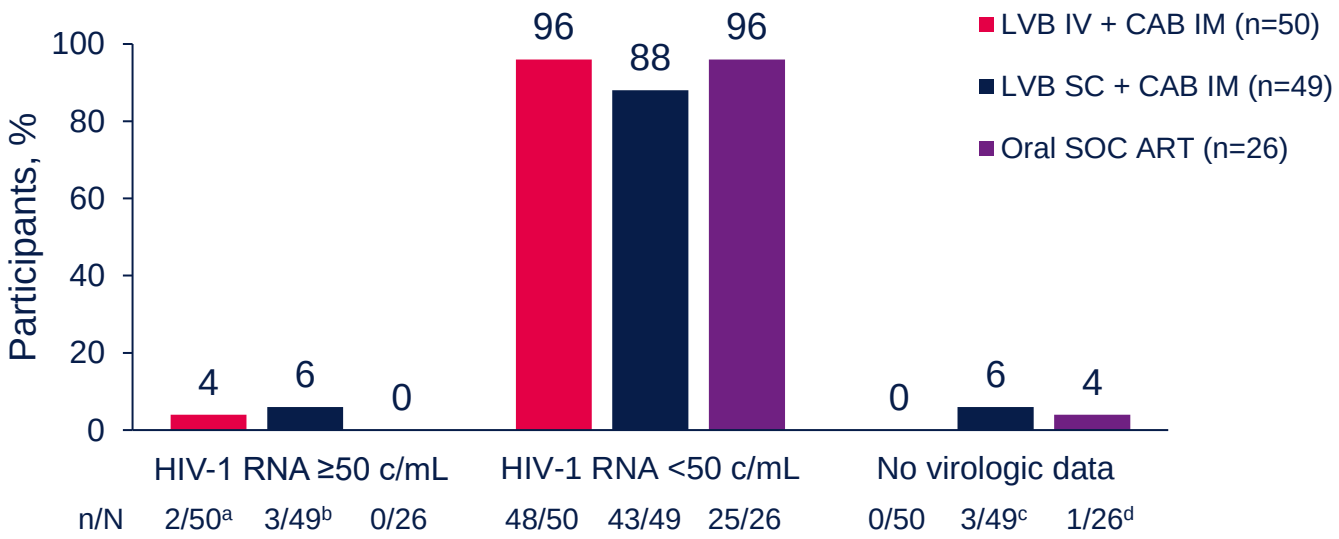
Demographics and Baseline Characteristics Were Well Balanced Across Groups

Parameter	LVB IV + CAB IM (n=50)	LVB 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)
BMI, 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)
LVB 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; BMI, body mass index; CAB, cabotegravir; IC_{90}, 90% inhibitory concentration; INSTI, integrase strand transfer inhibitor; IM, intramuscular; IV, intravenous; LVB, lotivibart; 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 LVB (IC_{90} ≤2.0 µg/mL) per inclusion criteria.

LVB + CAB IM Maintained Virologic Suppression in a High Proportion of Adults With Baseline LVB Sensitivity

Efficacy at Month 6 (FDA Snapshot, full analysis set)



ART, antiretroviral therapy; CAB, cabotegravir; FDA, US Food and Drug Administration; IM, intramuscular; IV, intravenous; LVB, lotivibart; 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).

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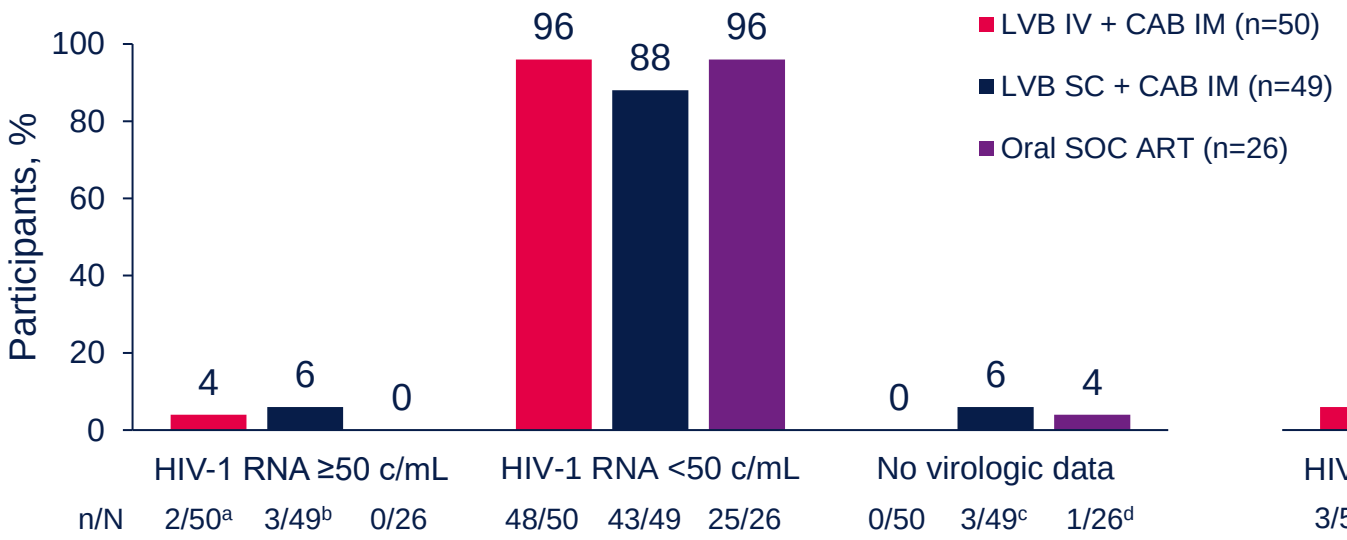
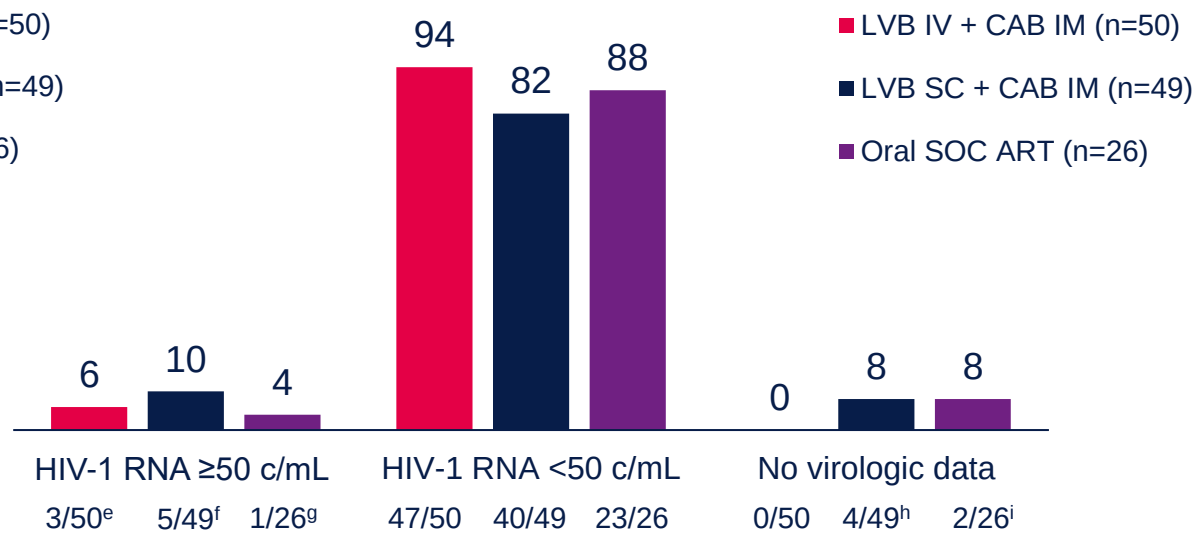


Efficacy at Month 12 (FDA Snapshot, full analysis set)



- CD4+ cell count remained stable around baseline values and no trends for median change were observed through Month 12

ART, antiretroviral therapy; CAB, cabotegravir; FDA, US Food and Drug Administration; IM, intramuscular; IV, intravenous; LVB, lotivibart; 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). [e]n=1 data in window not below threshold and n=2 discontinued for lack of efficacy. [f]n=3 data in window not below threshold and n=2 discontinued for lack of efficacy. [g]n=1 data in window not below threshold. [h]n=3 discontinued study due to adverse event and n=1 discontinued for other reasons (participant withdrawal). [i]n=1 discontinued for other reasons (participant withdrawal) and n=1 on study but missing data in window.

No Participants in the LVB IV Group Met CVF Between Months 6 and 12

	LVB IV + CAB IM (n=50)		LVB SC + CAB IM (n=49)			Oral SOC ART (n=26)
Parameter	**Participant 1**	**Participant 2**	**Participant 1**	**Participant 2**	**Participant 3**	**Participant 1[a]**
Baseline LVB IC_{90}, µg/mL	1.26	0.60	0.80	0.94	**1.26**	—
Baseline INSTI RAMs	None	None	None	None	**None**	None
Time of rebound	Month 3	Month 6	Month 3	Month 1[e]	**Month 12**	Month 9
HIV-1 RNA at CVF, c/mL	1810	3200	363,000	1290	**114,000**	214
LVB IC_{90} at CVF, µg/mL[b]	>50	3.34	1.08[c]	0.66[f]	**11.98**	—
CAB RAMs at CVF[b]	None	None	Q148R[d]	None	**T97A, N155H**	L74I[g]
CAB fold-change at CVF[b]	0.52	1.34	2.17	1.33	**2.60**	0.58

- LVB SC group: 2 participants met CVF by Month 6; there was 1 additional CVF by Month 12
- No participants in the LVB IV group and 2 participants in the LVB SC group had CAB RAMs at CVF
- 3/5 participants in LVB groups had baseline LVB IC_{90} ≤1 µg/mL; phenotypic sensitivity alone does not explain CVF
- 3/5 participants developed reduced sensitivity to LVB at CVF (IV, n=2; SC, n=1)

Data are bolded for participant 3 in the LVB SC group to emphasize that CVF occurred after Month 6. ART, antiretroviral therapy; CAB, cabotegravir; CVF, confirmed virologic failure; IC_{90}, 90% inhibitory concentration; IM, intramuscular; INSTI, integrase strand transfer inhibitor; IV, intravenous; LVB, lotivibart; RAM, resistance-associated mutation; SC, subcutaneous; SOC, standard of care; SVF, suspected virologic failure.

[a]Participant had treatment interruption due to insurance access issue between Months 8 and 10. Oral SOC ART was bictegravir/emtricitabine/tenofovir alafenamide. [b]CVF defined as 2 consecutive HIV-1 RNA measurements ≥200 c/mL. [c]LVB IC_{90} at SVF (defined as a single HIV-1 RNA measurement ≥200 c/mL) was 1.08; at post-CVF, LVB IC_{90} was 2.15, which exceeds protocol-defined phenotypic cutoff of ≤2 µg/mL for sensitivity to LVB. Measurement occurred after CVF at the discontinuation visit ~1 month after SVF and ~1 week after CVF. [d]Q148R was detected after CVF at the discontinuation visit and was detected at a frequency of 0.56% at baseline. [e]At Month 1 + 2 weeks. [f]At SVF. [g]Relevant to subtype A6 only.

No Clinically Significant AEs Were Observed After Month 6 in the LVB Groups

- LVB IV and SC were generally well tolerated through 12 months; no LVB/CAB-related AEs caused withdrawal in the IV group, and no LVB/CAB-related serious AEs occurred
- No serious or severe immune reactions, including anaphylaxis and cytokine release syndrome, or neutropenia occurred
- No clinically meaningful laboratory abnormalities were attributed to LVB
- Safety and tolerability of CAB LA IM QM were consistent with the product label
- Rates of ISRs did not increase between Month 6 (data not shown) and Month 12

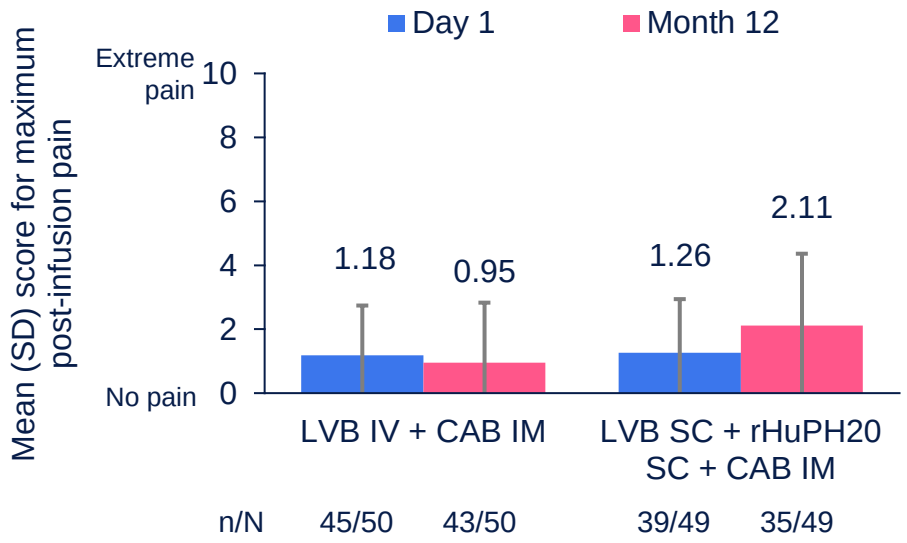
Participants, n (%)[a]	LVB IV + CAB IM (n=50)	LVB SC + CAB IM (n=49)	Oral SOC ART (n=26)
Any AE[b]	46 (92)	45 (92)	18 (69)
Grade 1-2	36 (72)	26 (53)	16 (62)
Grade 3	8 (16)	17 (35)	1 (4)
Grade 4	2 (4)	2 (4)	1 (4)
Any LVB/CAB-related AE	34 (68)	32 (65)	—
Grade 3	0	10 (20)[c]	—
Grade 4	0	0	—
Participants reporting any LVB-related ISR	4 (8)	25 (51)	—
Any LVB/CAB-related AE excluding ISRs	14 (28)	7 (14)	—
Occurring in ≥10% of participants			
Fatigue	6 (12)	1 (2)	—
Any serious AE	2 (4)	5 (10)	2 (8)
LVB/CAB-related serious AEs	0	0	—
LVB/CAB-related AEs leading to withdrawal	0	3 (6)[d]	—

AE, adverse event; ART, antiretroviral therapy; CAB, cabotegravir; ISR, infusion-site reaction; IM, intramuscular; IV, intravenous; LA, long-acting; LVB, lotivibart; QM, monthly; SC, subcutaneous; SOC, standard of care.

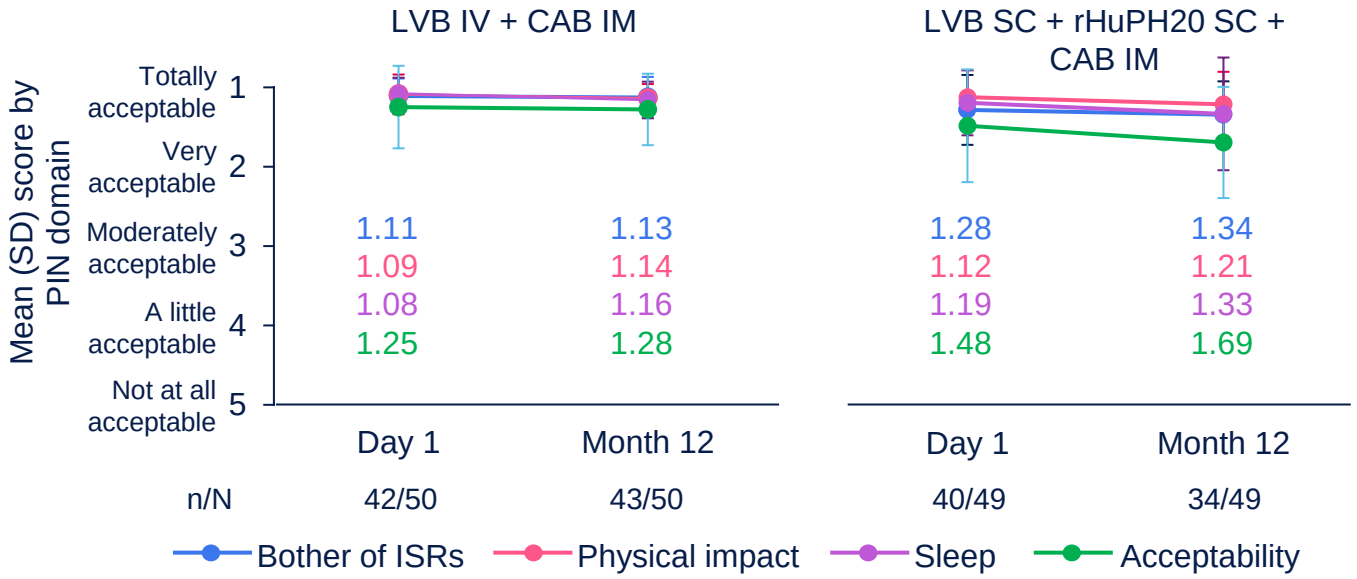
[a]Safety data in table are from Month 12. [b]AEs occurring in ≥10% of participants receiving LVB IV include injection-site pain, fatigue, COVID-19, increased lipase, and headache. AEs occurring in ≥10% of participants receiving LVB SC include infusion-site erythema, injection-site pain, infusion-site pain, infusion-site induration, infusion-site swelling, and injection-site nodule. [c]Includes infusion-site erythema (n=7), infusion-site swelling (n=3), infusion-site induration (n=2), injection-site pain (n=1), and injection-site sterile abscess (n=1). [d]Includes LVB/CAB-related anxiety and depression (n=1), CAB-related injection-site pain (n=1), and CAB-related injection-site abscess and cellulitis (n=1).

Participants Reported Low Pain and High Tolerability

Numeric rating scale (pain) scores by treatment group[a]



Perception of injection (tolerability) scores by domain[a]



- Mean NRS pain scores for the IV group remained very low from Day 1 to Month 12; for the SC group, mean NRS pain scores remained low but increased by <1 point through Month 12
- Mean PIN scores across all domains remained “very” to “totally acceptable” throughout the study, with negligible changes from Day 1 to Month 12

CAB, cabotegravir; IM, intramuscular; ISR, infusion-site reaction; IV, intravenous; LVB, lotivibart; NRS, numeric rating scale; PIN, perception of injection; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

[a]Findings were sustained from Day 1 to Month 12.

Conclusions

At 12 months, LVB with CAB LA maintained virologic suppression, demonstrating durable efficacy in an adult population with baseline LVB sensitivity

- LVB IV demonstrated a more favorable safety and tolerability profile than LVB SC
  - No new safety signals or additional AEs were identified between Month 6 and Month 12
- These findings support the continued evaluation of LVB IV Q6M with CAB LA IM Q2M in part 2 of EMBRACE, which is fully enrolled
- LVB is part of ViiV Healthcare's broader efforts to develop innovative ultra-long-acting therapies that address the diverse needs of people affected by HIV and transform HIV care

Plain language summary

In this year-long study, lotivibart, an experimental HIV medicine still in development, kept the virus under control and was safe and well tolerated. Lotivibart was given every 4 months, and when given through a vein, it was better tolerated than when given under the skin. This treatment was studied alongside cabotegravir, another HIV medicine given as an injection in the muscle, every month

AE, adverse event; CAB, cabotegravir; IM, intramuscular; IV, intravenous; LA, long-acting; LVB, lotivibart; Q2M, every 2 months; Q6M, every 6 months; SC, subcutaneous.

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