Injectable HIV-1 Capsid Inhibitor VH4011499 (VH-499) Formulation Supports Ultra-Long-Acting Dosing

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Background

- Advancing long-acting antiretrovirals is essential to expanding treatment options, providing more convenient choices that improve adherence, ensuring a good tolerability profile with minimal drug–drug interactions, enhancing quality of life, and driving progress toward ending the HIV epidemic[1,2]
- VH-499 is a new HIV-1 capsid inhibitor in development as a potential ultra-long-acting injectable antiretroviral
  - Monotherapy demonstrated highly potent antiviral activity in persons with HIV-1 naive to ART, with up to a mean maximum viral load reduction of -2.2 $\log_{10}$ c/mL through 11 days[3]
  - Well tolerated across a range of single and multiple oral doses[3,4]
  - No inhibition or induction of CYP3A4[4]
- Here we present interim safety and PK findings from a FTiH study assessing the ultra-long-acting potential of an injectable VH-499 formulation

ART, antiretroviral therapy; FTiH, first-time-in-humans; PK, pharmacokinetics; VH-499, VH4011499.

1. Ullah Nayan et al. *Adv Drug Deliv Rev*. 2023;200:115009. **2.** Vinay et al. *HIV Med*. 2025;26:1343-1355. **3.** Griesel et al. CROI 2025; San Francisco, CA. Oral presentation 153. **4.** Thakkar et al. *Infect Dis Ther*. 2025;14:1011-1025.

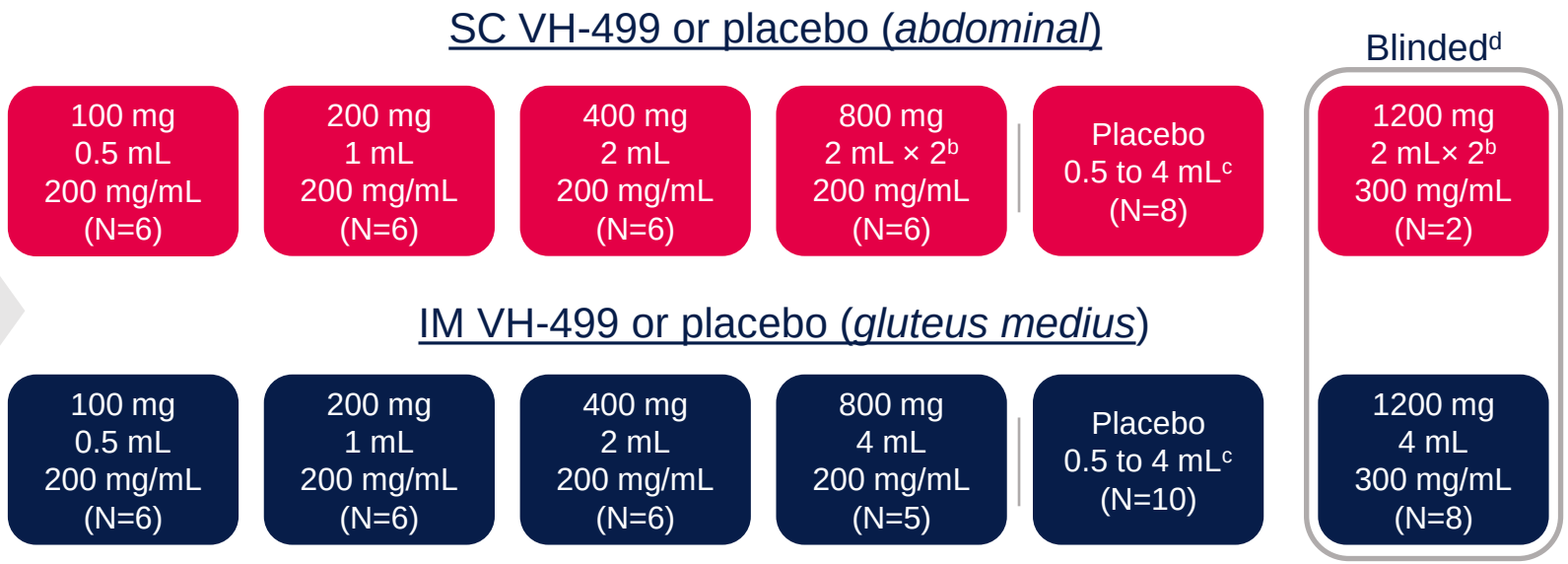
Study Design

An ongoing double-blind, randomized, placebo-controlled, adaptive, phase 1 study (NCT06724640)

Part A: Single ascending doses of SC or IM VH-499 solution[a] or matching placebo

Inclusion criteria

- Aged 18-55 years
- Adults without HIV-1
- Body weight >50 kg
- BMI 18-32 kg/m^2



Endpoints

- Safety,[e] tolerability, and PK were assessed post-dose, with follow-up through Week 78[f]
- Single-dose PK parameters using available data were evaluated by non-compartmental analyses

BMI, body mass index; IM, intramuscular; PK, pharmacokinetics; SC, subcutaneous; VH-499, VH4011499.

[a]Data collection is ongoing for additional SC and IM cohorts. [b]Given as a split injection in opposite abdominal quadrants. [c]Placebo matched the injection volumes and number of injections of the VH-499 cohorts. [d]Cohorts are currently blinded with ongoing data collection; only PK data for these cohorts are presented herein. [e]Assessed using the Division of AIDS grading scale. [f]Follow-up duration varies across cohorts due to staggered start-up timelines, with data collection ongoing.

Participant Demographics and Baseline Characteristics

- A total of 32 and 33 participants were enrolled in the SC and IM cohorts, respectively (VH-499 and placebo; shown below)
- Most participants were male[a] (92% [60/65]), 35% (23/65) identified as Black, median age was 36 years, and median BMI was 26.0 kg/m^2

	SC					IM					
Parameter	**100 mg 0.5 mL (N=6)**	**200 mg 1 mL (N=6)**	**400 mg 2 mL (N=6)**	**800 mg 2 mL × 2 (N=6)**	**Placebo 0.5 to 4 mL (N=8)**	**100 mg 0.5 mL (N=6)**	**200 mg 1 mL (N=6)**	**400 mg 2 mL (N=6)**	**800 mg 4 mL (N=5)**	**Placebo 0.5 to 4 mL (N=10)**	**Total (N=65)**
Age, median (range), y	38 (30-48)	31 (18-46)	33 (22-42)	34 (21-39)	36 (23-51)	31 (27-45)	36 (29-42)	42 (29-50)	35 (29-55)	37 (25-55)	36 (18-55)
Male, n (%)[a]	6 (100)	6 (100)	6 (100)	6 (100)	7 (88)	6 (100)	6 (100)	4 (67)	4 (80)	9 (90)	60 (92)
Race, n (%)											
Asian	0	0	0	1 (17)	0	0	0	1 (17)	0	0	2 (3)
Black	4 (67)	0	0	4 (67)	4 (50)	1 (17)	2 (33)	2 (33)	2 (40)	4 (40)	23 (35)
White	2 (33)	5 (83)	5 (83)	0	3 (38)	5 (83)	3 (50)	2 (33)	3 (60)	5 (50)	33 (51)
Multiple races	0	1 (17)	1 (17)	1 (17)	1 (13)	0	1 (17)	1 (17)	0	1 (10)	7 (11)
Ethnicity, Hispanic or Latine, n (%)	2 (33)	2 (33)	2 (33)	0	3 (38)	4 (67)	2 (33)	1 (17)	1 (20)	3 (30)	20 (31)
BMI, median (range), kg/m^2	24.7 (20.1-28.9)	26.4 (20.9-29.5)	26.5 (22.4-29.2)	25.9 (19.9-31.6)	27.6 (22.0-32.0)	27.6 (25.0-31.5)	26.7 (22.5-28.9)	24.2 (20.8-32.0)	23.0 (21.9-26.8)	26.8 (24.8-30.1)	26.0 (19.9-32.0)

BMI, body mass index; IM, intramuscular; SC, subcutaneous; VH-499, VH4011499.

[a]Assigned male sex at birth.

ISRs Predominantly Mild and None Led to Discontinuation

- Among participants receiving VH-499, 87% (41/47) experienced 1 or more ISRs overall, with injection-site pain as the most common ISR (83% [39/47]); ISRs were predominantly grade 1 (79% [37/47]) and transient (median duration, 1-4 days across cohorts)
- The ISR profile of the IM 1200-mg cohort (blinded) is similar to that of prior IM cohorts

	SC						IM					
AE, n (%)	100 mg 0.5 mL (N=6)	200 mg 1 mL (N=6)	400 mg 2 mL (N=6)	800 mg 2 mL × 2 (N=6)	Placebo 0.5 to 4 mL (N=8)	VH-499 total SC (N=24)	100 mg 0.5 mL (N=6)	200 mg 1 mL (N=6)	400 mg 2 mL (N=6)	800 mg 4 mL (N=5)	Placebo 0.5 to 4 mL (N=10)	VH-499 total IM (N=23)
Any ISR	5 (83)	6 (100)	6 (100)	6 (100)	5 (63)	23 (96)	5 (83)	5 (83)	3 (50)	5 (100)	4 (40)	18 (78)
Maximum grade 1	5 (83)	6 (100)	3 (50)	6 (100)	5 (63)	20 (83)	5 (83)	5 (83)	3 (50)	4 (80)	3 (30)	17 (74)
Maximum grade 2[a]	0	0	2 (33)	0	0	2 (8)	0	0	0	1 (20)	1 (10)	1 (4)
Maximum grade 3[a]	0	0	1 (17)	0	0	1 (4)	0	0	0	0	0	0
Maximum grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Leading to withdrawal[b]	0	0	0	0	0	0	0	0	0	0	0	0
Most common ISRs[c]												
Injection-site pain	5 (83)	6 (100)	4 (67)	6 (100)	2 (25)	21 (88)	5 (83)	5 (83)	3 (50)	5 (100)	3 (30)	18 (78)
Injection-site erythema	0	1 (17)	5 (83)	1 (17)	2 (25)	7 (29)	0	0	0	1 (20)	1 (10)	1 (4)
Injection-site swelling	3 (50)	0	3 (50)	1 (17)	1 (13)	7 (29)	0	0	0	2 (40)	1 (10)	2 (9)
Injection-site nodule[d]	0	0	3 (50)	2 (33)	1 (13)	5 (21)	0	0	0	2 (40)	0	2 (9)

Note: Data from 1200-mg cohorts are not included as cohorts remain blinded; only PK data from these cohorts are shown in this presentation. AE, adverse event; IM, intramuscular; ISR, injection-site reaction; SC, subcutaneous; VH-499, VH4011499.

[a]All grade 2 and 3 ISRs were of injection-site swelling; the grade 3 ISR of injection-site swelling in the SC 400-mg cohort had a duration of 2 days. [b]Per protocol, participants were encouraged to continue in the study if they experienced a potential drug-related AE, laboratory abnormality, electrocardiogram change, or toxicity event, with their AE managed, if appropriate, and followed to resolution. [c]Additional ISRs included injection-site bruising (SC 200 mg, n=1; SC 800 mg, n=2; IM placebo, n=1), injection-site discoloration (SC placebo, n=1), injection-site hemorrhage (SC placebo, n=1), injection-site pruritus (SC 100 mg, n=1), injection-site hypoesthesia (SC 400 mg, n=1), and injection-site edema (SC placebo, n=1). [d]Median duration of resolved ISR nodules in the SC cohorts ranged from 9.5 to 32.5 days (9.5 days [SC 400 mg], 32.5 days [SC 800 mg], and 29.0 days [SC placebo]), compared with 3.5 days in the IM 800-mg cohort.

VH-499 Was Well Tolerated and Had a Favorable Safety Profile

- All VH-499–related non-ISR AEs were mild, none were serious, and no participants withdrew for safety reasons
- There were no trends in non-ISR AEs, and no grade 2-4 non-ISR AEs were related to VH-499
- No clinically significant trends in laboratory tests, vital signs, or electrocardiogram parameters were observed

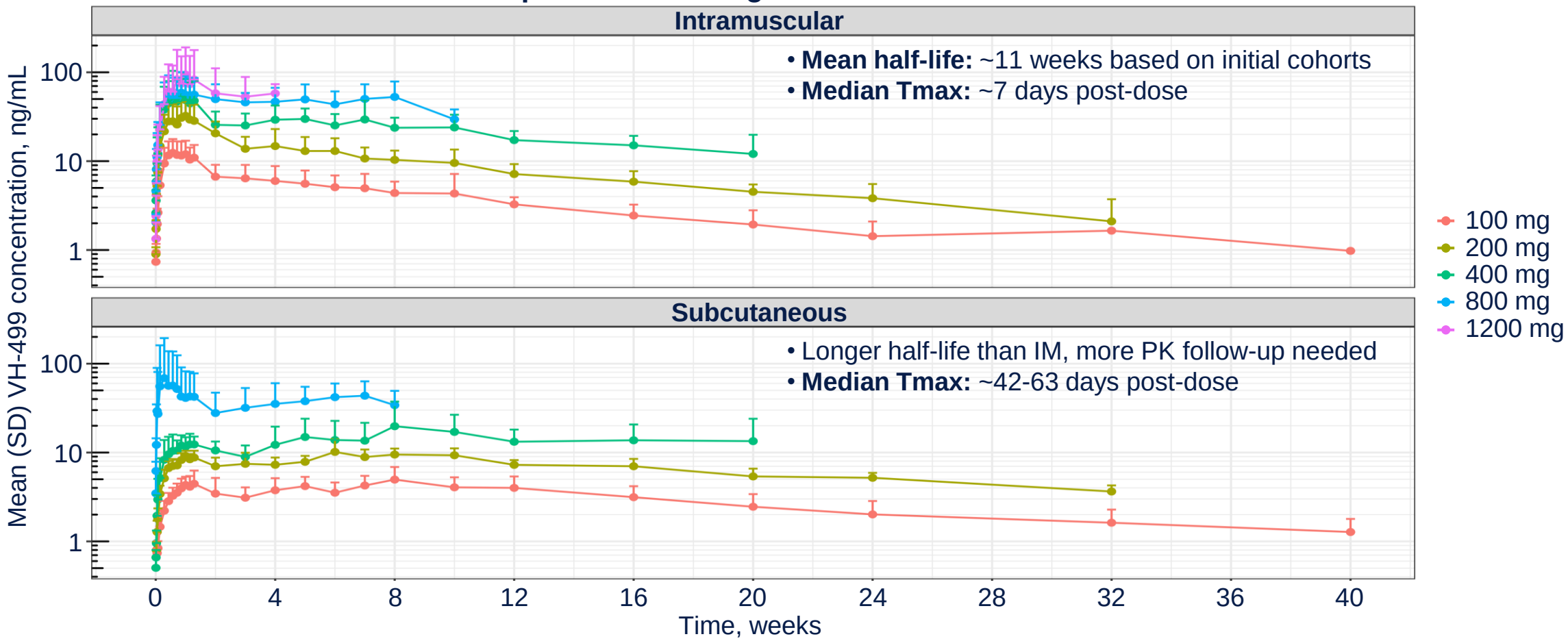
	SC						IM					
Non-ISR AEs (regardless of causality), n (%)	**100 mg 0.5 mL (N=6)**	**200 mg 1 mL (N=6)**	**400 mg 2 mL (N=6)**	**800 mg 2 mL × 2 (N=6)**	**Placebo 0.5 to 4 mL (N=8)**	**VH-499 total SC (N=24)**	**100 mg 0.5 mL (N=6)**	**200 mg 1 mL (N=6)**	**400 mg 2 mL (N=6)**	**800 mg 4 mL (N=5)**	**Placebo 0.5 to 4 mL (N=10)**	**VH-499 total IM (N=23)**
Any non-ISR AE	2 (33)	2 (33)	6 (100)	4 (67)	3 (38)	14 (58)	3 (50)	4 (67)	4 (67)	3 (60)	5 (50)	14 (61)
Grade 1	2 (33)	1 (17)	6 (100)	3 (50)	2 (25)	12 (50)	2 (33)	4 (67)	3 (50)	3 (60)	4 (40)	12 (52)
Grade 2	0	0	0	1 (17)	0	1 (4)	0	0	0	0	0	0
Grade 3	0	1 (17)[a]	0	0	0	1 (4)	1 (17)[c]	0	0	0	1 (10)[e]	1 (4)
Grade 4	0	0	0	0	1 (13)[b]	0	0	0	1 (17)[d]	0	0	1 (4)
Any serious AE	0	0	0	0	0	0	0	0	0	0	0	0
Any AE leading to withdrawal[f]	0	0	0	0	0	0	0	0	0	0	0	0

AE, adverse event; AST, aspartate aminotransferase; IM, intramuscular; ISR, injection-site reaction; SC, subcutaneous; VH-499, VH4011499.

[a]Grade 3 AE of increased AST not related to VH-499. [b]Grade 4 AE of increased blood creatinine phosphokinase not related to placebo. [c]Grade 3 AE of increased blood triglycerides not related to VH-499. [d]Grade 4 AE of increased blood creatinine phosphokinase not related to VH-499. [e]Grade 3 AE of diarrhea not related to placebo. [f]Per protocol, participants were encouraged to continue in the study if they experienced a potential drug-related AE, laboratory abnormality, electrocardiogram change, or toxicity event, with their AE managed, if appropriate, and followed to resolution.

VH-499 Demonstrated Long Half-Life Following IM and SC Dosing

Concentration-vs-time profiles following administration of IM or SC VH-499[a]

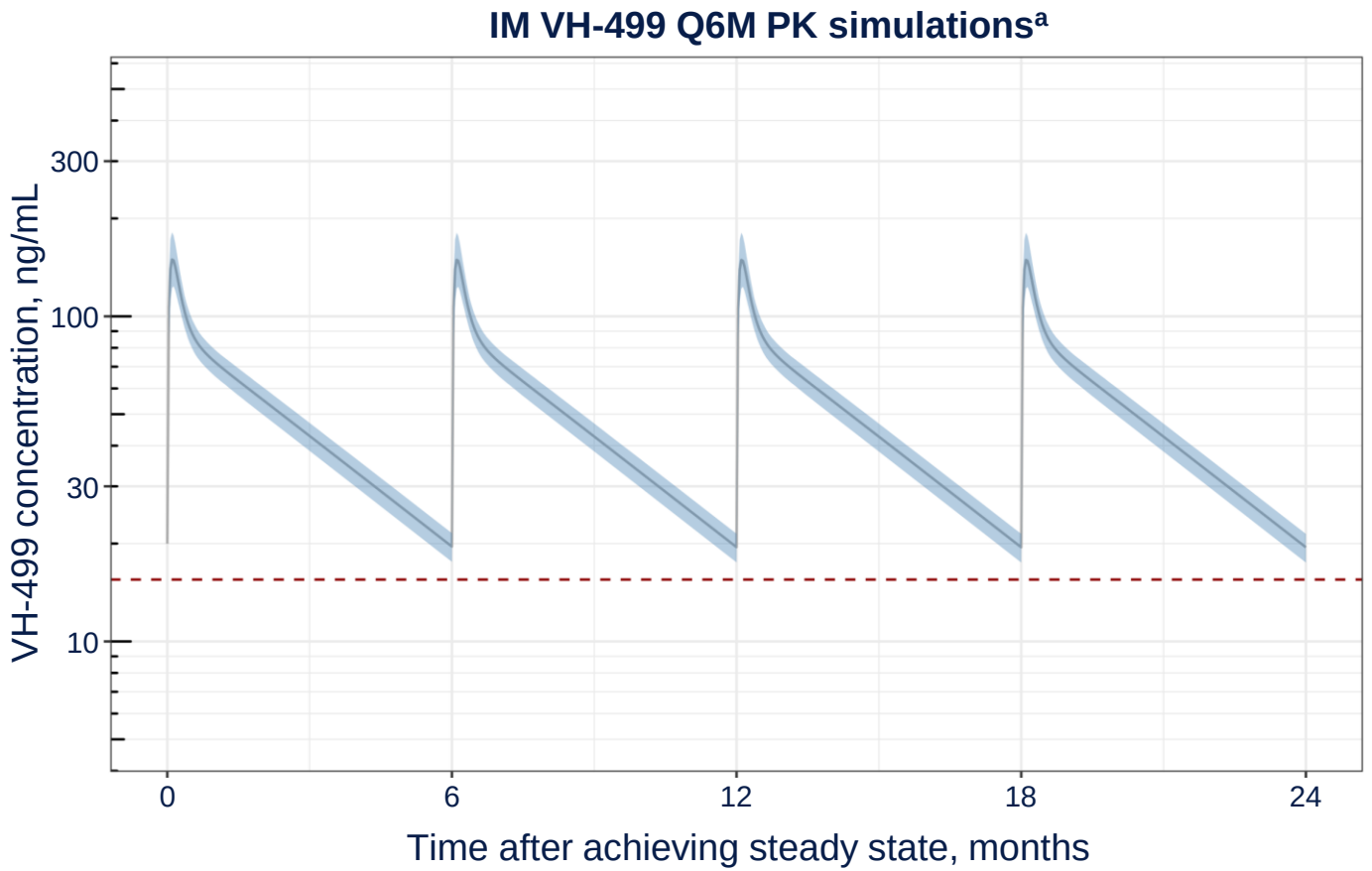


IM, intramuscular; PK, pharmacokinetics; SC, subcutaneous; Tmax, time to maximum plasma concentration; VH-499, VH4011499.

[a]Participants with VH-499 concentration below the lower limit of quantification (0.5 ng/mL) had concentration value imputed to zero. If imputed values were >30%, then SD was not calculated.

VH-499 Simulations Support Twice-Yearly Dosing

- Preliminary PopPK simulations indicate that twice-yearly IM maintenance dose is within the range of doses currently evaluated in a FTiH study[1]
- VH-499 exposures are projected to rapidly achieve target concentrations within the first 48 hours after initiation of IM dosing
- Modeling approaches, along with emerging PK and safety data, will be used to further optimize VH-499 development



EC_{90}, 90% maximal concentration; FTiH, first-time-in-humans; IM, intramuscular; PK, pharmacokinetics; PopPK, population PK; Q6M, every 6 months; VH-499, VH4011499.

[a]PopPK-based simulations using available IM VH-499 PK data to date; a simple loading and maintenance dose Q6M starting at Month 1 is expected to achieve 90% CIs of mean VH-499 exposures that are above the trough target EC_{90} of 15.5 ng/mL (red dashed line).

1. Thakkar et al. CROI 2026; Denver, CO. Poster 492.

Conclusions

VH-499 demonstrated a long half-life following IM and SC administration, supporting the goal of twice-yearly dosing

- Both IM and SC single-dose injections of VH-499 were well tolerated, with mild and transient ISRs that did not lead to study withdrawals
- These data support further evaluation of ultra-long-acting injectable VH-499 in the phase 2b study (CINERGY) in adults with HIV-1 naive to ART, anticipated to start in the second half of 2026
- VH-499 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

For more information on the PK-PD relationship between VH-499 and viral load reduction, see Thakkar et al. CROI 2026; Denver, CO. Poster 492

Plain language summary

VH-499 is an experimental medicine being studied for HIV. In this study, we found that it can stay in the body for a long time, which means it might only need to be given twice a year as an injection into the muscle or under the skin. It was also generally well tolerated and had a good safety profile

ART, antiretroviral therapy; IM, intramuscular; ISR, injection-site reaction; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; VH-499, VH4011499.

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