Safety, Tolerability, and Acceptability of HIV-1 Capsid Inhibitor VH4011499 Injectable Formulation

P041

Bronagh Shepherd,[1] Veronica Bainbridge,[1] Jose R. Castillo-Mancilla,[2] Nilay Thakkar,[3] Gilda Bontempo,[4] Adelaide Jewell,[5] Jia Chang,[6] Shawn L. Searle,[7] Noopur Singh,[3] Lisa Morgan,[8] Babafemi Taiwo,[2] Paul Benn[5]

[1]GSK, London, UK; [2]ViiV Healthcare, Durham, NC, USA; [3]GSK, Collegeville, PA, USA; [4]ViiV Healthcare, Branford CT, USA; [5]ViiV Healthcare, London, UK; [6]Trialmed, Austin, TX, USA; [7]Trialmed, Las Vegas, NV, USA; [8]GSK, Amersfoort, Netherlands

Please scan the QR code for additional resources

Key Takeaways

- **VH4011499 (VH-499) is a new capsid inhibitor in development for long-acting treatment of HIV-1, with potential for twice-yearly dosing**
- **We report interim safety and participant-reported outcomes from a first-time-in-human study in adults without HIV after VH-499 was administered subcutaneously (SC) or intramuscularly (IM) as single or multiple doses**
- **Long-acting VH-499 demonstrated a favorable safety and tolerability profile administered as either SC or IM doses**
- **Participant-reported post-injection pain was transient, and local reactions and pain were generally acceptable**

Plain Language Summary

- VH-499 is an experimental long-acting medicine being studied for the treatment of HIV. It may only need to be given twice a year, as an injection either under the skin or into the muscle
- In this study, VH-499 was generally well tolerated, with no serious drug-related side effects and no one dropping out of the study due to side effects. Injection-site pain was brief, and participants rated the injections as generally acceptable
- These results support further study of VH-499 together with other long-acting medicines as a complete treatment for HIV. The CINERGY study (NCT07816250) will test VH-499 in adults with HIV who have not yet started HIV treatment

Introduction

- VH4011499 (VH-499) is a new capsid inhibitor, with the potential for twice-yearly dosing, in development as a long-acting treatment for people with HIV-1[1]
- Oral VH-499 monotherapy demonstrated highly potent antiviral activity in people with HIV-1 naive to antiretroviral therapy and has been well-tolerated across all studies to date[1-3]
- VH-499 has shown no inhibition or induction of cytochrome P450 3A4[2]
- Interim safety, pharmacokinetic (PK), tolerability, and acceptability findings of long-acting VH-499 are presented here

Methods

- In an ongoing phase 1, double-blind (sponsor-unblind), randomized, placebo-controlled, adaptive study (NCT06724640), adults without HIV in the United States were randomized to receive long-acting injectable VH-499 or placebo:
  - Single ascending doses (100-1800 mg) via subcutaneous (SC) administration (abdomen; any split injections were given in opposite abdominal quadrants)
  - Single ascending doses (100-1500 mg) via intramuscular (IM) administration (*gluteus medius*)
  - Repeat doses via IM (*gluteus medius*) administration (600 mg on Day 1 and 1200 mg on Day 29)
- VH-499 was administered at concentrations of 200 or 300 mg/mL, with a maximum volume per injection of 3 mL for SC administration and 5 mL for IM administration; pre-injection ice packs were used for cohorts receiving doses ≥800 mg
- The primary endpoints were safety, tolerability, and PK
  - Single-dose PK parameters using available data were evaluated by non-compartmental analyses
- Participant-reported outcomes were exploratory endpoints:
  - Acceptance of pain and injection-site reactions (ISRs) and bother by pain assessed using the Perception of Injection questionnaire
  - Injection-site pain assessed using the Numeric Rating Scale

Results

Baseline Demographics and Characteristics

- Overall, 122 participants received long-acting injectable VH-499 or placebo as either single SC (n=48), single IM (n=49), or repeat IM (n=25) injections
- Most participants were male sex at birth (81% [99/122]) and 48% (59/122) identified as a race other than White

Safety Outcomes

- Most adverse events (AEs) were mild or moderate in severity (Tables 1 and 2)
- VH-499–related AEs were primarily ISRs, most commonly injection-site pain (84% [77/92]); median ISR duration ranged from 1 to 5 days across all cohorts
- There were no withdrawals due to AEs and no serious or grade 4 VH-499–related AEs
- No clinically significant trends in laboratory tests, vital signs, or electrocardiogram parameters were observed

Table 1. ISR Summary[a]

ISR, n (%)	VH-499 single dose SC: 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)	1200 mg 2 mL × 2 (N=6)	1800 mg 3 mL × 2 (N=6)	PBO 0.5-6 mL (N=12)	Total SC VH-499 (N=36)
Any ISR	5 (83)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	9 (75)	35 (97)
Maximum grade 1	5 (83)	6 (100)	3 (50)	6 (100)	6 (100)	5 (83)	9 (75)	31 (86)
Maximum grade 2	0	0	2 (33)	0	0	1 (17)	0	3 (8)
Maximum grade 3-4	0	0	1 (17)[b]	0	0	0	0	1 (3)
Most common ISRs[c]								
Injection-site pain	5 (83)	6 (100)	4 (67)	6 (100)	6 (100)	6 (100)	5 (42)	33 (92)
Injection-site erythema	0	1 (17)	5 (83)	1 (17)	0	4 (67)	3 (25)	11 (31)
Injection-site swelling	3 (50)	0	3 (50)	1 (17)	2 (33)	5 (83)	3 (25)	14 (39)
Injection-site nodule[d]	0	0	4 (67)	3 (50)	4 (67)	6 (100)	2 (17)	17 (47)

ISR, n (%)	VH-499 single dose IM: 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)	1200 mg 4 mL (N=6)	1500 mg 5 mL (N=6)	PBO 0.5-5 mL (N=14)	Total IM VH-499 (N=35)	VH-499 repeat doses IM[e]: D1: 600 mg 2 mL D29: 1200 mg 4 mL (N=21)	PBO 2-4 mL (N=4)
Any ISR	5 (83)	5 (83)	3 (50)	5 (100)	6 (100)	4 (67)	5 (36)	28 (80)	19 (90)	2 (50)
Maximum grade 1	5 (83)	5 (83)	3 (50)	4 (80)	6 (100)	3 (50)	4 (29)	26 (74)	19 (90)	2 (50)
Maximum grade 2	0	0	0	1 (20)	0	1 (17)	1 (7)	2 (6)	0	0
Maximum grade 3-4	0	0	0	0	0	0	0	0	0	0
Most common ISRs[c]										
Injection-site pain	5 (83)	5 (83)	3 (50)	5 (100)	4 (67)	4 (67)	4 (29)	26 (74)	18 (86)	2 (50)
Injection-site erythema	0	0	0	0	0	0	1 (7)	0	0	0
Injection-site swelling	0	0	0	2 (40)	0	0	1 (7)	2 (6)	1 (5)	0
Injection-site nodule[f]	0	0	0	1 (20)	1 (17)	0	0	2 (6)	2 (10)	0

D, day; PBO, placebo. [a]Pre-injection ice packs were used for cohorts dosed ≥800 mg. [b]A grade 3 AE of injection-site swelling that resolved in 2 days and was related to VH-499. [c]Occurring in ≥50% of participants in any cohort. [d]Median durations (days) of resolved ISR nodules in the SC cohorts were 117.5 (400 mg), 62.0 (800 mg), 85.0 (1200 mg), 8.0 (1800 mg), and 36.0 (PBO). [e]VH-499 administered as 600 mg on Day 1 and 1200 mg on Day 29. At data cutoff of this interim analysis, 20 participants received 2 injections in the VH-499 group, and 3 participants received 2 injections in the placebo group. [f]Median durations (days) of resolved ISR nodules in the IM cohorts were 3.0 (800 mg), 35.0 (1200 mg), and 8.0 (600 mg → 1200 mg).

Table 2. Safety Summary

AE, n (%)	VH-499 single dose SC: 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)	1200 mg 2 mL × 2 (N=6)	1800 mg 3 mL × 2 (N=6)	PBO 0.5-6 mL (N=12)	Total SC VH-499 (N=36)
Any non-ISR AE	3 (50)	3 (50)	6 (100)	5 (83)	4 (67)	4 (67)	7 (58)	25 (69)
Maximum grade 1	2 (33)	1 (17)	6 (100)	3 (50)	3 (50)	2 (33)	6 (50)	17 (47)
Maximum grade 2	1 (17)	0	0	2 (33)	1 (17)	1 (17)	0	5 (14)
Maximum grade 3-4	0	2 (33)[a]	0	0	0	1 (17)[b]	1 (8)[c]	3 (8)
Any serious AE	0	1 (17)[d]	0	0	0	0	0	1 (3)

AE, n (%)	VH-499 single dose IM: 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)	1200 mg 4 mL (N=6)	1500 mg 5 mL (N=6)	PBO 0.5-5 mL (N=14)	Total IM VH-499 (N=35)	VH-499 repeat doses IM[e]: D1: 600 mg 2 mL D29: 1200 mg 4 mL (N=21)	PBO 2-4 mL (N=4)
Any non-ISR AE	3 (50)	4 (67)	4 (67)	3 (60)	4 (67)	4 (67)	9 (64)	22 (63)	12 (57)	3 (75)
Maximum grade 1	2 (33)	4 (67)	3 (50)	3 (60)	4 (67)	4 (67)	7 (50)	20 (57)	10 (48)	2 (50)
Maximum grade 2	0	0	0	0	0	0	0	0	1 (5)	1 (25)
Maximum grade 3-4	1 (17)[f]	0	1 (17)[g]	0	0	0	2 (14)[h]	2 (6)	1 (5)[i]	0
Any serious AE	0	0	0	0	0	0	0	0	0	0

D, day; PBO, placebo. [a]Grade 3 non–drug-related AEs of increased aspartate aminotransferase and back pain. [b]Grade 3 non–drug-related AE of increased lipase. [c]Grade 4 non–PBO-related AE of increased creatine kinase. [d]Serious non–drug-related AE of back pain. [e]VH-499 administered as 600 mg on Day 1 and 1200 mg on Day 29. At data cutoff of this interim analysis, 20 participants received 2 injections in the VH-499 group, and 3 participants received 2 injections in the placebo group. [f]Grade 3 non–drug-related AE of increased blood triglycerides. [g]Grade 4 non–drug-related AE of increased creatine kinase. [h]Grade 3 non–PBO-related AE of diarrhea and grade 4 non–PBO-related AE of increased lipase. [i]Grade 4 non–drug-related AE of increased lipase.

Acknowledgments: This study was funded by ViiV Healthcare. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by Fingerpaint Medical and funded by ViiV Healthcare.

References: 1. Thakkar et al. CROI 2026; Denver, CO. Oral presentation 175. **2.** Thakkar et al. *Infect Dis Ther*. 2025;14:1011-1025. **3.** Griesel et al. *Clin Infect Dis*. 2026 [Epub ahead of print].

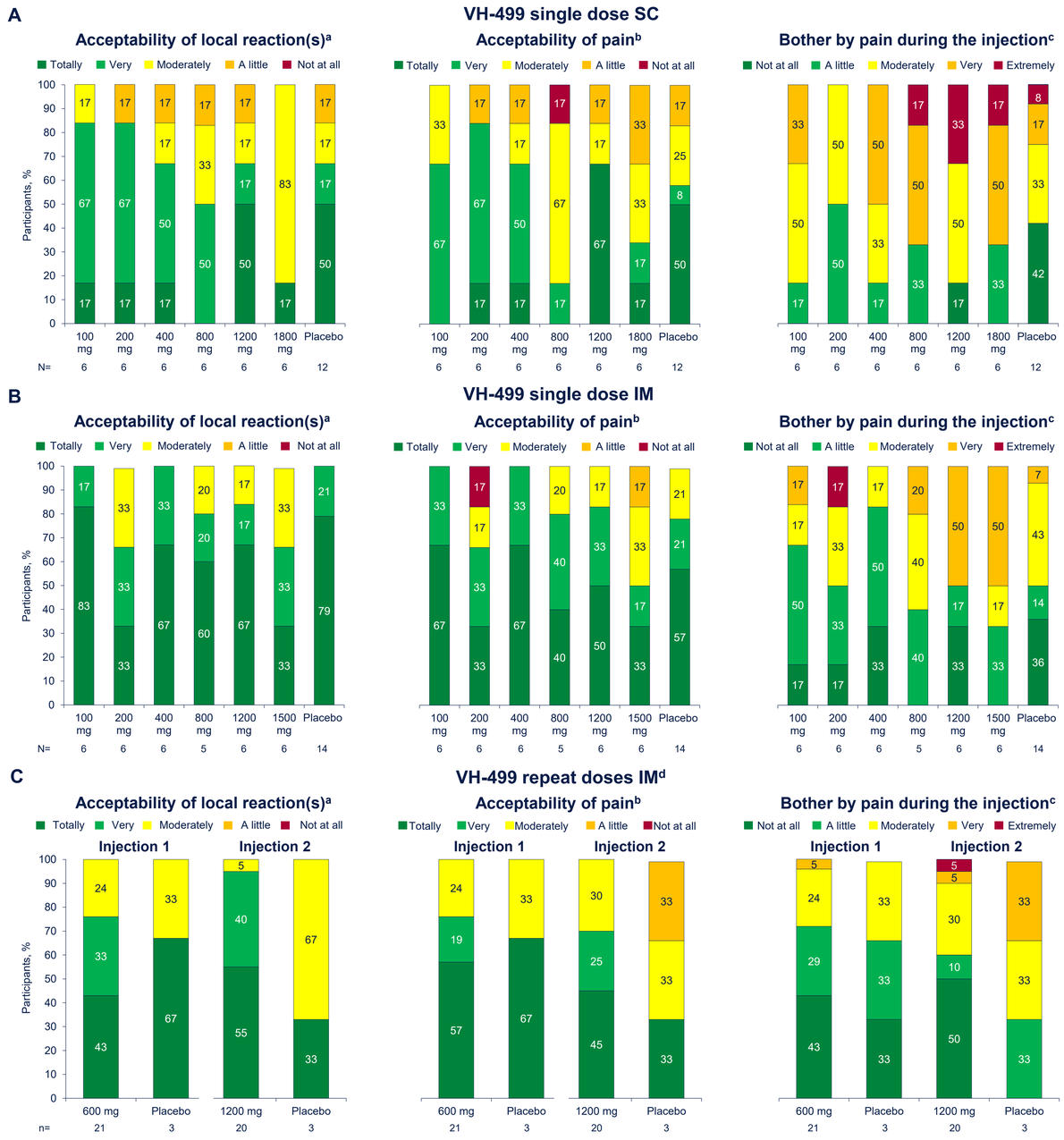
PK

- VH-499 had a long half-life following SC and IM administration based on initial cohorts[1]
  - IM administration: VH-499 had a mean half-life of approximately 11 weeks and a median time to maximum plasma concentration (Tmax) of approximately 7 days post-dose
  - SC administration: VH-499 had a longer half-life than with IM administration, with a median Tmax of approximately 42-63 days post-dose

Participant-Reported Outcomes

- Most participants rated local reactions and post-injection pain as totally/very acceptable (Figure 1)

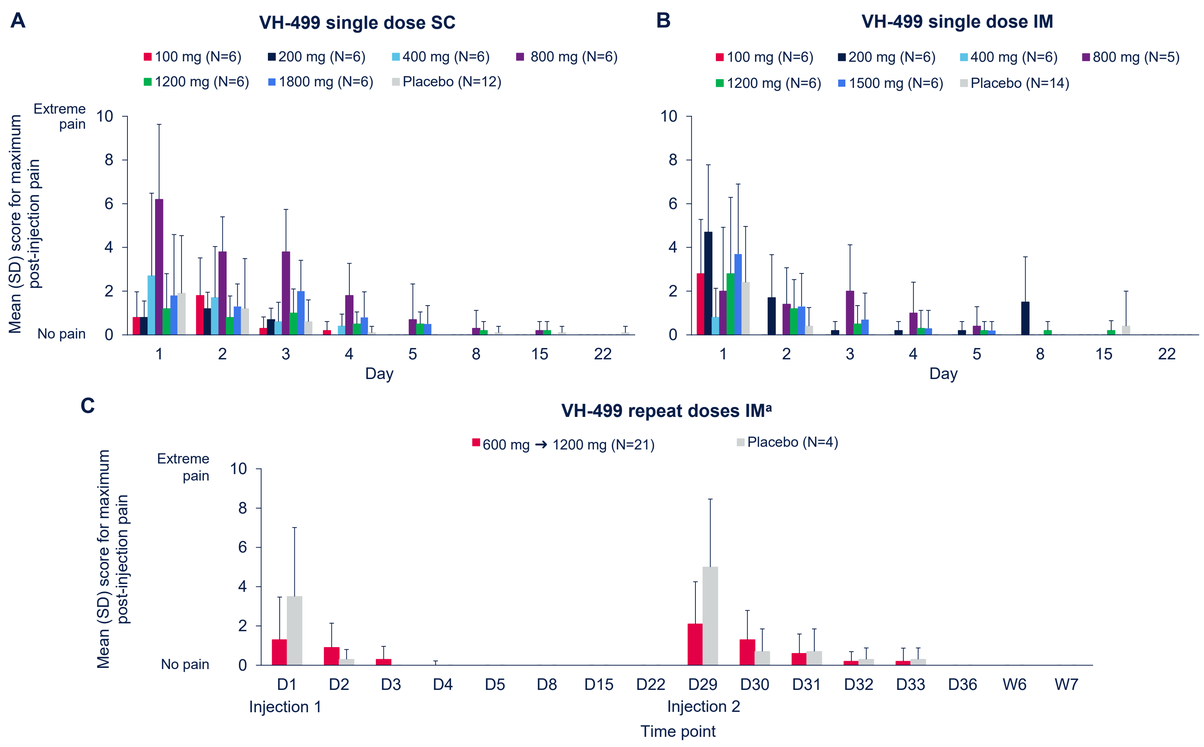
Figure 1. PIN Responses for (A) Single Doses of SC VH-499, (B) Single Doses of IM VH-499, and (C) Repeat Doses of IM VH-499



PIN questionnaire administered on Day 8 for single doses and Days 8 and 36 for repeat doses; 3 items on the questionnaire were completed to explore overall acceptability of injections and pain. PIN, Perception of Injection. [a]Participants responded to: "How acceptable was/were your local reactions?" [b]Participants responded to: "How acceptable was your pain?" [c]Participants responded to: "How bothered were you by pain during the injection?" [d]VH-499 administered as 600 mg on Day 1 and 1200 mg on Day 29. At data cutoff of this interim analysis, 20 participants received 2 injections in the VH-499 group, and 3 participants received 2 injections in the placebo group.

- Self-reported pain was mild to moderate and transient (Figure 2)

Figure 2. NRS Scores Indicating Post-Injection Pain for (A) Single Doses of SC VH-499 (B) Single Doses of IM VH-499, and (C) Repeat Doses of IM VH-499



The NRS ranges from 0 ("no pain") to 10 ("extreme pain") and was completed within 30-60 minutes on the day of dosing and on Days 2, 3, 4, 5, 8, 15, and 22 after dosing. D, day; NRS, Numeric Rating Scale; W, week. [a]VH-499 administered as 600 mg on Day 1 and 1200 mg on Day 29. At data cutoff of this interim analysis, 20 participants received 2 injections in the VH-499 group, and 3 participants received 2 injections in the placebo group.

Conclusions

- Both SC and IM VH-499 formulations demonstrated a favorable safety and tolerability profile with no VH-499–related serious AEs or withdrawals
- VH-499 demonstrated a long half-life following SC and IM administration, supporting the possibility of twice-yearly dosing
- Post-injection pain was transient and local reactions and pain were rated as generally acceptable
- Findings support further evaluation of a complete long-acting regimen containing VH-499 in the phase 2b CINERGY study in adults with HIV-1 naive to treatment (NCT07816250)

Presenting author: Jose R. Castillo-Mancilla; jose.r.castillomancilla@viivhealthcare.com