Population PK and Exposure-Response Analysis of Orally Administered VH4011499 in People With HIV-1

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Plain Language Summary

- VH4011499 (VH-499) is a new long-acting HIV medicine that reduced levels of the virus in people with HIV who were not previously treated and was well tolerated in early studies
- We used data from earlier studies and generated models to show that higher levels of VH-499 in the body are strongly linked to bigger drops in HIV levels. This helps us understand which VH-499 doses should be tested in future clinical trials

Introduction

- Advancing long-acting antiretrovirals is essential to expand treatment options, offer more convenient and sustainable choices that improve adherence and quality of life, and accelerate progress toward ending the HIV epidemic[1]
- VH-499 is an HIV-1 capsid inhibitor currently in development as a long-acting injectable antiretroviral agent for HIV-1[1,2]
- In a phase 1 first-in-human trial of adults without HIV, orally administered VH-499 was well tolerated, demonstrated a long oral half-life ranging from 51-66 hours, and did not inhibit or induce CYP3A4[2]
- In a proof-of-concept (PoC) phase 2a trial of adults with HIV-1, orally administered VH-499 monotherapy was well tolerated and demonstrated rapid and highly potent antiviral activity (mean maximum decline, 2.2 $\log_{10}$ c/mL)[1]
- Here, we describe VH-499 pharmacokinetics (PK) and its exposure–HIV-1 RNA response relationship to inform target exposures and dose selection for future clinical studies

Methods

- Data included in the analysis were obtained from studies of orally administered VH-499, including 2 phase 1 studies among participants without HIV (NCT05393271: 6 participants in moderate-fat state receiving 200-mg single-dose tablet; NCT06368986: 48 participants in fasted and high-fat states receiving 25- and 200-mg tablets) and a phase 2a, placebo-controlled, PoC study among participants with HIV-1 who were treatment-naive (NCT06039579: 20 participants in moderate-fat state receiving 25 mg [n=7], 100 mg [n=6], or 250 mg [n=7] on Days 1 and 6 over 11 days of monotherapy)[1,2]
- A population PK (PopPK) model was developed to characterize VH-499 tablet PK following oral administration
- Model selection was guided by standard model criteria, utilizing diagnostic plots and visual predictive checks
- Exposure-response analysis was performed using relevant PoC data, including maximum HIV-1 RNA reduction from baseline vs VH-499 concentration at Day 11 using a maximal effect (E_{max}) model
- When VH-499 concentration data at Day 11 were unavailable, PopPK model–predicted exposures were employed
- Model-based evaluation of the PK-PD relationship was supported by a prior knowledge of the viral load dynamics of lenacapavir (ie, there is a shared model structure and E_{max} for both VH-499 and lenacapavir)

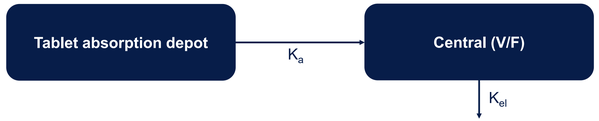
Using a PopPK model and PoC study data, we determined that there is a strong PK-PD relationship between concentration of VH-499 (HIV-1 capsid inhibitor) and HIV-1 RNA viral load reduction, providing evidence to inform dose selection for future VH-499 clinical trials

Results

PopPK Model Development

- The final PopPK model was a 1-compartment model of disposition with first-order absorption of the tablet formulation (Figure 1)
  - Covariate effects of relative bioavailability of the tablet in various food states were included
- Bioavailability of VH-499 was decreased in the fasted state compared with the fed state (Table 1)

Figure 1. Schematic of Structural Model



A 1-compartment model with first-order linear elimination and first-order absorption of tablet. CL/F, apparent clearance; K_a, first-order absorption rate constant; K_{el}, first-order elimination rate constant ([CL/F]/[V/F]); V/F, apparent volume of distribution.

Table 1. Final PopPK Model Parameters

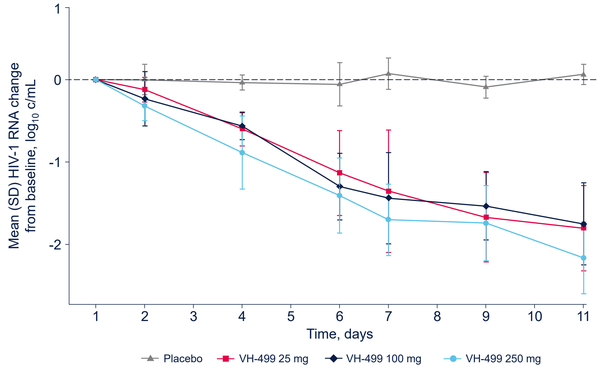
Parameter	Final parameter estimate		
	Typical value	RSE, %	Shrinkage, %
Fixed effects			
First-order rate constant of tablet absorption, h^{-1}	0.154	6.8	—
CL/F, L/h	36.2	9.7	—
V/F, L	2660	10	—
Covariate effects			
Relative bioavailability $_{\text{tablet, high fat}}$	3.38	14.5	—
Relative bioavailability $_{\text{tablet, moderate fat}}$	3.62	14.4	—
Relative bioavailability $_{\text{fasted}}$	0.237	13.7	—
Stochastic model			
IIV CL/F, CV%[a]	28.3	11.6	23
IIV in $K_{a\ \text{tablet}}$, CV%	32.3	34.3	35
IIV in bioavailability $_{\text{tablet}}$, CV%	46.4	16.7	5
Proportional residual error, SD	0.313	4.7	—

CL/F, apparent clearance; IIV, interindividual variability; K_a, first-order absorption rate constant; RSE, relative standard error; V/F, apparent volume of distribution. [a]IIV expressed as % coefficient of variation (CV% = $\sqrt{(\exp(\omega 2)-1)*100}$, where $\omega 2$ is the variance of the interindividual random effect).

Viral Load Analysis

- VH-499 exposure showed a strong relationship with HIV-1 RNA decline (Figure 2)
  - Each VH-499 group exhibited highly potent antiviral activity; no reduction of viral load was observed in the placebo group
  - For the VH-499 25-, 100-, and 250-mg groups, a mean maximum decline of 1.8, 1.8, and 2.2 $\log_{10}$ c/mL was observed, respectively
- Additional analyses demonstrated that the maximum reduction from baseline in HIV-1 RNA was independent of the viral load before initiation of treatment with VH-499

Figure 2. Mean (SD) HIV-1 RNA Change From Baseline vs Time

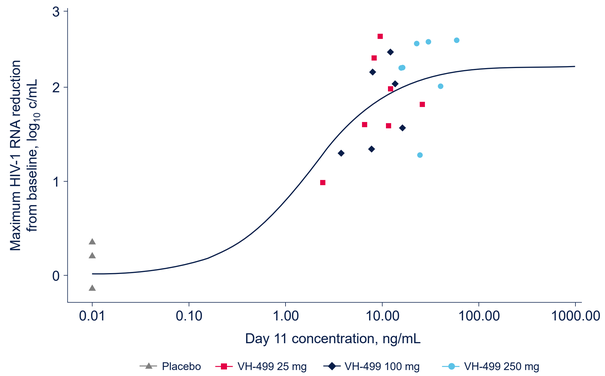


Horizontal dashed line represents zero change from baseline.

PK-PD Analysis

- The PK-PD relationship of maximal reduction from baseline vs Day 11 concentration was quantified under the assumption of an E_{max} relationship, where the E_{max} of VH-499 is equivalent to lenacapavir (2.2)[3]
- A simple E_{max} model with Day 11 concentration adequately described the VH-499 exposure-response relationship (Figure 3)
- The 90% maximal concentration (EC_{90}) derived from the VH-499 PK-PD model is similar to the published lenacapavir EC_{90} (12.6 ng/mL; Table 2)

Figure 3. Maximum HIV-1 RNA Reduction From Baseline vs Day 11 Concentration



Model-predicted individual participant exposures to VH-499 are presented when a Day 11 concentration was not available. Placebo data were assigned a concentration of 0.01 ng/mL to allow visualization on a log-transformed x-axis. Dosing was done on Day 1 and Day 6.

Table 2. Parameter Summary of PK-PD Relationship for Day 11 Concentration vs Maximum HIV-1 RNA Reduction From Baseline

Relationship	Parameter	Estimate[a]
Model derived from VH-499 data collected in PoC study	E_{max}	2.2 FIXED
	EC_{50}	1.78 ng/mL
	EC_{90}	15.5 ng/mL[b]

EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal concentration; E_{max}, maximal effect. [a]Observed Day 11 concentration data were employed where available; otherwise, model-predicted individual subject Day 11 concentrations were obtained from the PopPK model and employed in the analysis. [b]Approximate concentration giving rise to EC_{90}.

Conclusions

- These models helped to characterize VH-499 PK and the strong PK-PD relationship between VH-499 concentration and HIV-1 RNA reduction from baseline
- Additionally, this analysis helped to identify VH-499 target exposures, which will be used to optimize dose selection for long-acting formulations in future VH-499 clinical trials
- For data on the first-in-human study assessing the long-acting potential of an injectable formulation of VH-499, please see oral presentation 175[4]

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