Third-Generation INSTI VH4524184 (VH-184) Has an Enhanced Resistance Profile vs Bictegravir

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Plain Language Summary

- VH4524184 (VH-184) is a new HIV medicine and is a kind of medicine currently available called an integrase inhibitor. VH-184 can work against viruses that have become resistant to other integrase inhibitors
- This study showed that in the laboratory, VH-184 has more activity against resistant HIV than that of a currently available integrase inhibitor called bictegravir (BIC)

Introduction

- Integrase strand transfer inhibitors (INSTIs) transformed HIV-1 care by delivering potent and durable virologic suppression combined with a high barrier to resistance
- Second-generation INSTIs are widely recommended as initial therapy for most people with HIV-1[1]; however, their widespread use necessitates development of newer INSTIs with even higher barriers to resistance
- VH-184 is the first third-generation INSTI being developed for HIV therapy
- VH-184 has demonstrated an enhanced in vitro resistance profile vs second-generation INSTIs, potent antiviral activity, and long-acting potential (see oral presentation 176)[2-4]

Methods

- Resistance profiles were evaluated against a panel of second-generation INSTI-resistant HIV-1 pseudotyped viruses derived from 14 participants who met confirmed virologic withdrawal criteria in the SAILING (n=7, through Week 132) and DAWNING (n=7, through Week 216) studies and 1 control participant

SAILING[5]

- Randomized, double-blind, phase 3, non-inferiority study
- Participants were treatment-experienced, naive to INSTIs, and on failing therapy with resistance to ≥2 antiretroviral therapy classes
- Randomized to receive dolutegravir 50 mg once daily or raltegravir 400 mg twice daily + background regimen

DAWNING[6]

- Randomized, open-label, phase 3b, non-inferiority study
- Participants were naive to INSTIs and protease inhibitors and on failing first-line therapy comprising a non-nucleoside reverse transcriptase inhibitor + 2 nucleoside reverse transcriptase inhibitors
- Randomized to receive dolutegravir 50 mg once daily or ritonavir-boosted lopinavir 800/200 mg once daily (or 400/100 mg twice daily) + 2 nucleoside reverse transcriptase inhibitors

- Population and clonal variants from on-treatment plasma samples were genotyped and tested in a phenotype assay
- Wild-type–level activity was defined as a half-maximal inhibitory concentration (IC_{50}) fold change (FC) ≤2
- A heat map showing the percentage of the population achieving a certain inhibitory quotient (IQ) coverage for clonal strains was created by combining exposure, with viral potency, and clonal FC
- Specifically, using a distribution of wild-type protein-adjusted 90% effective concentration ($PA\text{-}EC_{90}$), VH-184 and BIC trough concentrations (C_{tau}), and FC shifts in the clonal variants (ClonalFC), the individual IQ (IQ_i) was determined using the following formula:

$$IQ_i = C_{tau}/(PA\text{-}EC_{90i} \times ClonalFC)$$

VH-184 demonstrates lower fold changes and an enhanced resistance profile vs BIC, retaining activity against second-generation INSTI-resistant pseudotyped viruses

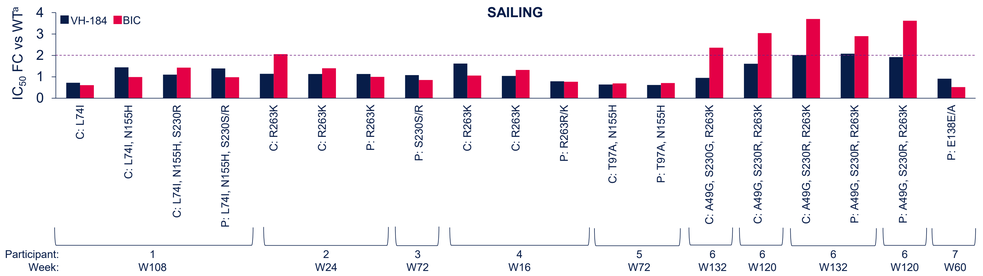
Results

- VH-184 demonstrated potent in vitro antiviral activity compared with BIC against viruses with emergent INSTI resistance from SAILING and DAWNING

SAILING

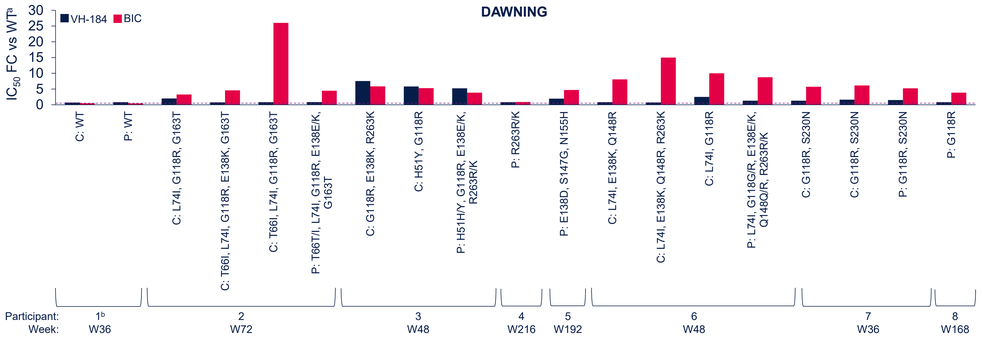
- When tested against pseudotyped virus populations and clonal variants from SAILING, VH-184 demonstrated retained activity vs BIC against viruses with multiple resistance mutations including R263K, S230G or S230R, and A49G, which increased BIC FC above wild-type level (ie, FC ≥2; Figure 1)

Figure 1. Antiviral Activity Against INSTI-Resistant Pseudotyped Virus Populations and Clonal Variants From SAILING



C, clonal variants; P, virus populations; W, week; WT, wild-type. [a]Wild-type–level activity defined as IC_{50} FC ≤2.

Figure 2. Antiviral Activity Against INSTI-Resistant Pseudotyped Virus Populations and Clonal Variants From DAWNING



C, clonal variants; P, virus populations; W, week; WT, wild-type. [a]Wild-type–level activity defined as IC_{50} FC ≤2. [b]This participant was used for WT virus (did not meet confirmed virologic withdrawal criteria).

DAWNING

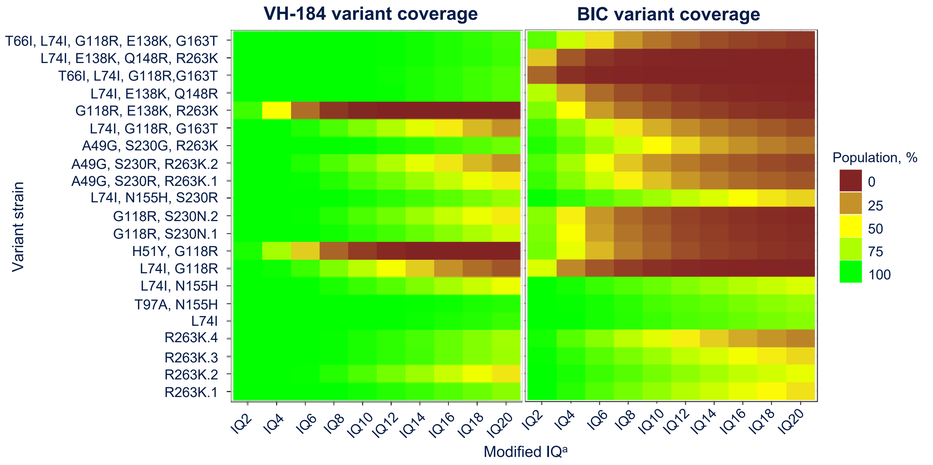
- When tested against pseudotyped virus populations and clonal variants from DAWNING, VH-184 showed retained activity vs BIC against G118R, either alone or in combination with additional substitutions (Figure 2)

- VH-184 also demonstrated lower FC against pseudotyped viruses harboring L74I, E138K, and/or G118R, as well as viruses with N155H, E138D, and S147G

Inhibitory Quotients for Clonal Variants

- Figure 3 illustrates the percentage of the population that achieves a certain IQ for each clonal strain
- VH-184 exposures combined with the enhanced resistance profile have the potential to demonstrate higher IQs across the breadth of mutant strains compared with BIC

Figure 3. Heat Map Depicting the Proportion of Individuals Achieving Each IQ for the Listed Clonal Variants



IQ, inhibitory quotient. [a]The IQ represents the ratio of drug exposure to viral susceptibility; IQ = (plasma drug concentration, C_{tau})/($PA\text{-}EC_{90}$ × ClonalFC).

Conclusions

- VH-184, a third-generation INSTI with potent antiviral activity and long-acting potential, demonstrated enhanced antiviral activity against second-generation INSTI-resistant pseudotyped viruses compared with BIC
  - The activity of VH-184 against a broader spectrum of INSTI-resistant viruses further demonstrates VH-184 as a third-generation INSTI
- These data further support the development of VH-184 as a core agent in a complete long-acting regimen; VH-184 is being evaluated in the phase 2b INNOVATE study (NCT07202546) and an ongoing phase 1 study assessing long-acting formulations (NCT06310551)
- Pharmacokinetics and evaluation of potential dosing regimens for long-acting VH-184 are being presented in oral presentation 176 by Back et al on Wednesday, February 25, 2026, at 10:00 AM[4]

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