Phase 1 Study of VH4524184 (VH-184), a New Third-Generation Integrase Strand Transfer Inhibitor (INSTI) With a Unique Resistance Profile

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25th International AIDS Conference; July 22-26, 2024; Munich, Germany

Disclosures

- Luise Rogg is an employee of ViiV Healthcare and holds GSK stocks

Introduction

- INSTIs have been the cornerstone of HIV-1 treatment for over 15 years[1]
  - The development of new INSTIs, including long-acting modalities that maintain a high barrier to resistance, is important to aid in the continued expansion of treatment options to meet the preferences of people living with HIV-1
- VH4524184 (VH-184) is a third-generation INSTI with long-acting potential in development for HIV-1 treatment
- In Poster WEPEB114, the in vitro antiviral potency of VH-184 was shown to be comparable to that of the second-generation INSTIs DTG and CAB, with a distinct resistance profile[2]
- Here, we present the safety, tolerability, and PK of VH-184 from a first-time-in-human study as well as the in vitro resistance profile of VH-184

CAB, cabotegravir; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; PK, pharmacokinetics; VH-184, VH4524184.

1. Isentress [US prescribing information]. Merck Sharp & Dohme LLC; 2022. **2.** Seki et al. AIDS 2024; Munich, Germany. Poster WEPEB114.

Study Design

Double-blind, randomized, placebo-controlled, phase 1, first-time-in-human study of VH-184

Inclusion criteria

- Aged 18-50 years
- Adults without HIV-1
- Body weight ≥50 kg
- BMI 18.5-32.0 kg/m^2

Part 1 SAD VH-184	N=9, doses administered after a moderate-fat meal				
	Cohort 1 **10 mg**	Cohort 2 **50 mg**	Cohort 3 **150 mg**	Cohort 4 **300 mg**	Cohort 5 **460 mg**
Part 2 MAD VH-184	Doses administered after a moderate-fat meal				
	Cohort 7 **160 mg QD** 14 days N=12		Cohort 8 **480 mg QD + MDZ 7.5 mg[a]** 14 days N=15		
Part 3 Food effect VH-184	Period 1 **100 mg** Fasted N=12 →	Washout period ≥15 days →	Period 2 **100 mg** Fed N=12		

Monitoring of

- Adverse events
- Vital signs
- Clinical laboratory values
- PK parameters

BMI, body mass index; MAD, multiple ascending dose; MDZ, midazolam; PK, pharmacokinetics; QD, once daily, SAD, single ascending dose; VH-184, VH4524184.

[a]VH-184 administered on Days 2-15; MDZ administered on Days 1 and 15.

Summary of Participant Demographics and Safety

- In the FTIH study, 84 participants were included (VH-184, n=63; placebo, n=21), all of whom completed the study
- 44 AEs were reported in 29 participants
- AEs were generally mild, and none were serious
- Drug-related AEs included eye pain, headache, fatigue, diarrhea, and constipation

Participant Demographics

Parameter	Part 1 (N=45)	Part 2 (N=27)	Part 3 (N=12)
Male sex, n (%)	41 (91)	26 (96)	12 (100)
Age, mean (SD), y	35.4 (8.1)	35.9 (6.7)	34.9 (8.6)
Race, n (%)			
White	18 (40)	16 (59)	4 (33)
Black or African American	21 (47)	7 (26)	6 (50)
Hispanic or Latin American ethnicity, n (%)	15 (33)	10 (37)	3 (25)
BMI, mean (SD), kg/m^2	25.8 (3.5)	26.3 (3.5)	26.4 (2.4)

Overview of AEs

	Part 1						Part 2			Part 3	
AEs, n (%)	10 mg (N=6)	50 mg (N=6)	150 mg (N=6)	300 mg (N=6)	460 mg (N=6)	Placebo (N=15)	160 mg QD (N=9)	480 mg QD/MDZ (N=12)	Placebo QD (N=6)	100 mg fasted (N=12)	100 mg fed (N=12)
Any AE	2 (33)	1 (17)	2 (33)	2 (33)	1 (17)	4 (27)	6 (67)	5 (42)	2 (33)	1 (8)	3 (25)
Grade 2-4	0	1 (17)	1 (17)	1 (17)	1 (17)	1 (7)	2 (22)	1 (8)	1 (17)	0	1 (8)
Drug-related AE	1 (17)	1 (17)	0	0	1 (17)	0	1 (11)	0	0	1 (8)	0
Grade 2-4	0	1 (17)	0	0	1 (17)	0	0	0	0	0	0
Elevated liver chemistry	0	0	1 (17)	1 (17)	0	0	1 (11)	0	0	0	1 (8)

AE, adverse event; BMI, body mass index; FTIH, first time in human; MDZ, midazolam; QD, once daily; VH-184, VH4524184.

Rogg et al. AIDS 2024; Munich, Germany. Oral presentation OAB2603.

Plasma VH-184 PK Parameters After Oral Administration of Single and Multiple Ascending Doses

- Geometric mean VH-184 plasma concentrations increased in a dose-proportional manner after single doses of 10 to 300 mg, without further increase after 460-mg single or 480-mg multiple doses
- Geometric mean half-life was ~24 hours
- Observed accumulation in exposures ranged from 1.3- to 1.9-fold after repeat VH-184 dosing of 480 and 160 mg, respectively
- Results of a geometric mean ratio test of MDZ and 1-hydroxymidazolam suggested that VH-184 had minimal impact on the PK of CYP3A substrates

Part 1: SAD					
VH-184 dose	**n**	**Cmax, µg/mL[a]**	**tmax, h[b]**	**$AUC_{0-\infty}$, h·µg/mL[a]**	**$t_{1/2}$, h[a]**
10 mg	6	0.9 (14.8)	6.0 (4.1-8.0)	28.0 (18.2)	22.1 (11.9)[c]
50 mg	6	4.4 (15.9)	5.0 (4.0-10.2)	134.7 (19.5)	24.1 (19.9)
150 mg	6	11.9 (20.4)	8.0 (4.0-8.1)	355.9 (46.2)	25.2 (26.2)
300 mg	6	23.7 (15.4)	8.0 (6.0-8.0)	745.7 (27.9)	24.5 (37.4)
460 mg	6	24.1 (21.7)	5.1 (4.0-10.0)	675.4 (29.3)	28.5 (42.3)
Part 2: MAD, Day 1/2					
VH-184 dose	**n**	**Cmax, µg/mL[a]**	**tmax, h[b]**	**AUC_{0-24h}, h·µg/mL[a]**	**$t_{1/2}$, h[a]**
160 mg QD	9	10.8 (20.8)	5.0 (4.0-10.1)	153.2 (19.1)	NC
480 mg QD/MDZ	12	23.5 (18.2)	5.6 (4.0-8.0)	348.9 (13.3)	NC
Part 2: MAD, Day 14/15					
VH-184 dose	**n**	**Cmax, µg/mL[a]**	**tmax, h[b]**	**AUC_{0-24h}, h·µg/mL[a]**	**$t_{1/2}$, h[a]**
160 mg QD	9	17.8 (22.6)	4.2 (4.0-6.1)	290.3 (26.9)	25.0 (17.8)
480 mg QD/MDZ	12	31.0 (23.3)	4.0 (3.1-7.9)	467.1 (21.3)	28.1 (33.3)

$AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 to infinity; AUC_{0-24h}, area under the plasma concentration–time curve from 0 to 24 hours; Cmax, maximum observed plasma concentration; %CVb, between-participant coefficient of variation; MAD, multiple ascending dose; MDZ, midazolam; NC, not calculated; PK, pharmacokinetics; QD, once daily; SAD, single ascending dose; $t_{1/2}$, terminal half-life; tmax, time to Cmax; VH-184, VH4524184.

[a]Values are geometric mean (%CVb). [b]Values are median (range). [c]n=5.

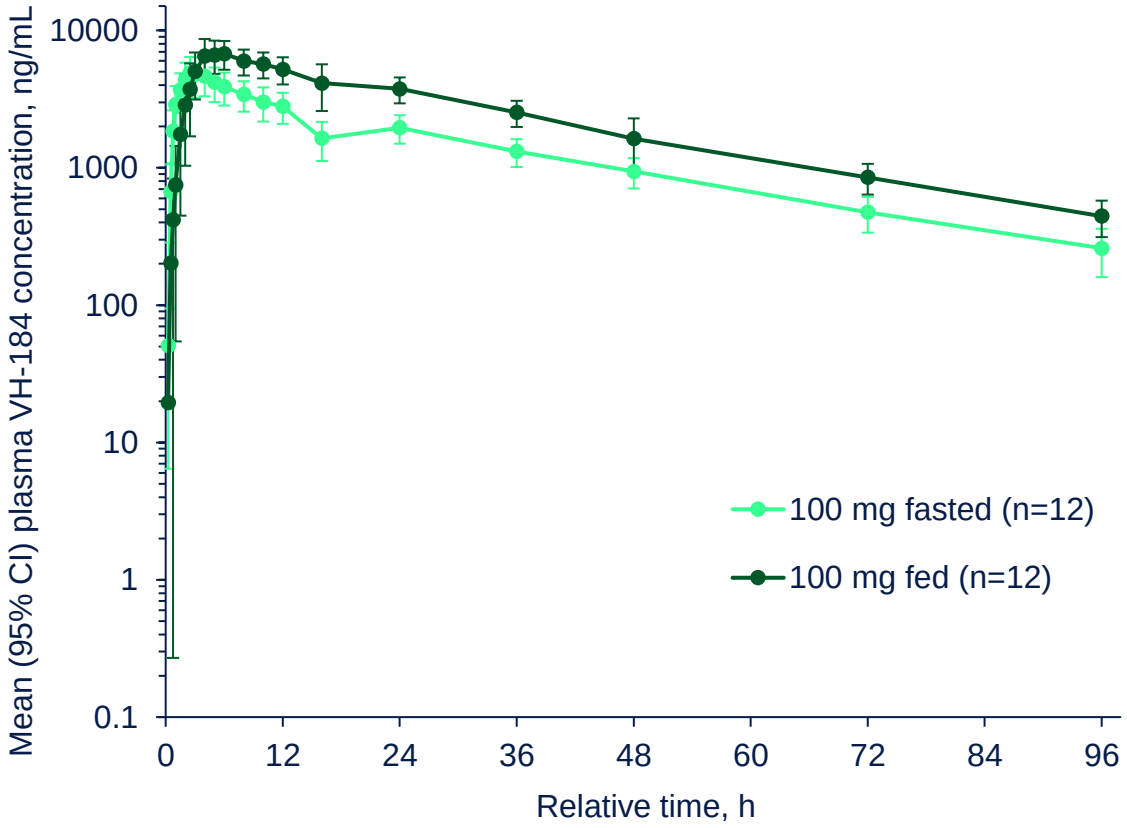
Rogg et al. AIDS 2024; Munich, Germany. Oral presentation OAB2603.

Plasma VH-184 PK Parameters After Oral Administration Under Fasted and Fed Conditions Indicate a Moderate Positive Food Effect

- PK parameters increased by 1.5- to 1.8-fold when comparing administration of VH-184 100 mg under fed vs fasted conditions

Part 3: Food effect

Parameter, geometric LS mean	VH-184 100 mg fed[a] (N=12)	VH-184 100 mg fasted (N=12)	Ratio (fed/fasted)	90% CI
$AUC_{0-\infty}$, h·µg/mL	221.7	125.7	1.8	1.3-2.4
AUC_{0-24h}, h·µg/mL	103.6	60.9	1.7	1.3-2.3
Cmax, µg/mL	7.3	5.0	1.5	1.1-1.9



$AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 to infinity; AUC_{0-24h}, area under the plasma concentration–time curve from 0 to 24 hours; Cmax, maximum observed plasma concentration; LS, least squares; PK, pharmacokinetics; VH-184, VH4524184.

[a]Meal of 800-1000 calories, with ~50% coming from fat, shortly before dosing.

Rogg et al. AIDS 2024; Munich, Germany. Oral presentation OAB2603.

Activity of VH-184 Against DTG-Selected INSTI-Resistant Viruses

- Resistance to VH-184 was evaluated in vitro against a panel of second-generation INSTI-resistant HIV-1 clinical isolate populations and clonal variants from SAILING and DAWNING

SAILING[1]

- Randomized, double-blind, phase 3, non-inferiority study
- Participants were treatment-experienced, naive to INSTIs, and on **failing therapy** with resistance to ≥2 ART classes
- Randomized to receive DTG 50 mg QD or RAL 400 mg BID + background regimen

DAWNING[2]

- Randomized, open-label, phase 3b, non-inferiority study
- Participants were naive to INSTIs and PIs, and on **failing first-line therapy** consisting of an NNRTI + 2 NRTIs
- Randomized to receive DTG 50 mg QD or LPV/r 800/200 mg QD (or 400/100 mg BID) + 2 NRTIs

Genotypic and phenotypic resistance testing was conducted for resistant isolate populations and representative clonal variants[a]

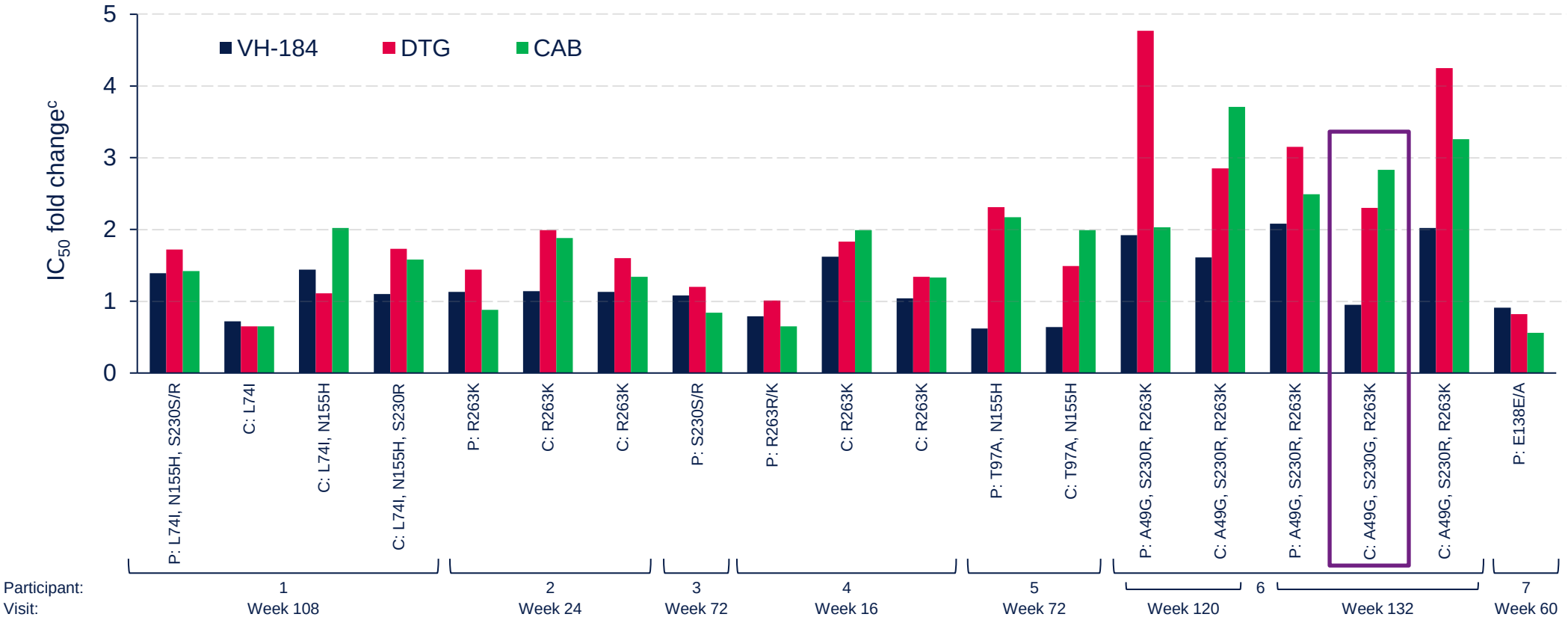
ART, antiretroviral therapy; BID, twice daily; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; LPV/r, ritonavir-boosted lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; QD, once daily; RAL, raltegravir; VH-184, VH4524184.

[a]Integrase substitutions specified for inclusion in isolate panel: A49G, H51Y, T66A/I/K, L68V/I, L74M/I, E92Q/V/G, Q95K, T97A, G118R, F121Y, E138A/K/D/T, G140A/C/S, Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K/T, G193E, S230R/N/G, and R263K.

1. Cahn et al. *Lancet*. 2013;382:700-708. **2.** Aboud et al. *Lancet Infect Dis*. 2019;19:253-264.

VH-184 Demonstrated Wild-Type–Level Antiviral Activity Against DTG-Selected Isolates With INSTI RAMs

Antiviral activity of VH-184 against a panel of HIV-1 clinical isolate populations[a] and clonal variants[b] from 7 participants in the phase 3 SAILING study



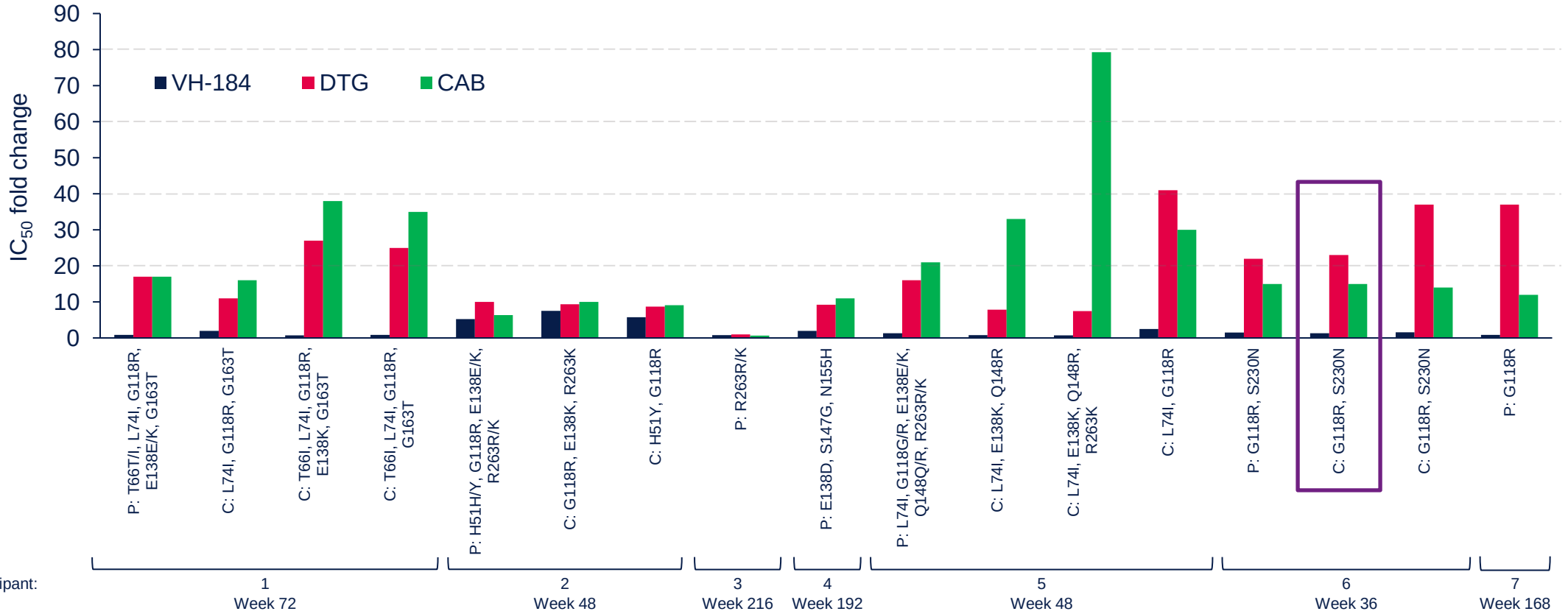
C, clonal variant; CAB, cabotegravir; DTG, dolutegravir; IC_{50}, half-maximal inhibitory concentration; INSTI, integrase strand transfer inhibitor; P, population; RAM, resistance-associated mutation; VH-184, VH4524184.

[a]Indicated with a "P" along the x-axis. [b]Indicated with a "C" along the x-axis. [c]A ≤2-fold change is wild-type–level activity.

Underwood et al. European HIV & Hepatitis Workshop 2015; Barcelona, Spain. Poster 6.

VH-184 Demonstrated Potent Antiviral Activity Against DTG-Selected INSTI-Resistant Isolates

Antiviral activity of VH-184 against a panel of HIV-1 clinical isolate populations[a] and clonal variants[b] from 7 participants in the phase 3 DAWNING study



C, clonal variant; CAB, cabotegravir; DTG, dolutegravir; IC_{50}, half-maximal inhibitory concentration; INSTI, integrase strand transfer inhibitor; P, population; VH-184, VH4524184.

[a]Indicated with a "P" along the x-axis. [b]Indicated with a "C" along the x-axis.

Underwood et al. *Antimicrob Agents Chemother*. 2022;66:e0164321.

Conclusions

- These data support the further development of VH-184 as a third-generation INSTI for HIV-1 treatment
  - VH-184 demonstrated a good safety and tolerability profile in this FTIH study
  - FTIH study results helped characterize VH-184 PK and indicate that VH-184 does not inhibit or induce CYP3A4 and has a moderate positive food effect, not dissimilar to DTG
- The in vitro resistance profile of VH-184 is distinct from that of prior INSTIs, retaining antiviral activity against second-generation INSTI-resistant clinical isolates
- VH-184 is being evaluated in an ongoing phase 2a proof-of-concept study in people living with HIV-1 who are naive to ART (NCT06214052) and an ongoing phase 1 FTIH study of long-acting injectable formulations in participants without HIV-1 (NCT06310551)

ART, antiretroviral therapy; DTG, dolutegravir; FTIH, first time in human; INSTI, integrase strand transfer inhibitor; PK, pharmacokinetics; VH-184, VH4524184.

Acknowledgments

- This study was funded by ViiV Healthcare
- The authors would like to thank the study participants, the investigators and site staff, and the ViiV Healthcare and GSK study team members
- Editorial assistance and graphic design support for this presentation were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare

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