Efficacy and Safety of the HIV-1 Maturation Inhibitor GSK3640254 + 2 NRTIs in Treatment-Naive Adults: 24-Week Results From the Phase IIb, Dose-Range Finding DOMINO Study

Samit R. Joshi,[1] Ezequiel Cordova,[2] Essack Mitha,[3] Antonella Castagna,[4] Moti Ramgopal,[5] Josep M. Llibre,[6] Anja Potthoff,[7] Oksana E. Chernova,[8] Sebastian A. Nuñez,[9] Choy Man,[10] Jerry L. Jeffrey,[10] Cindy Fishman,[11] James Oyee,[12] Aditya Joshi,[13] Ying Zhang,[11] Veronica Bainbridge,[12] Brian Wynne,[10] Max Lataillade[1]

[1]ViiV Healthcare, Branford, CT, USA; [2]Fundación IDEAA, Buenos Aires, Argentina; [3]Newtown Clinical Research Centre, Johannesburg, South Africa; [4]San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy; [5]Midway Immunology and Research Center, Fort Pierce, FL, USA; [6]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [7]Interdisciplinary Immunological Outpatient Clinic, Center for Sexual Health and Medicine, Department of Dermatology, Venereology and Allergology, Ruhr Universität Bochum, Bochum, Germany; [8]Samara Regional Clinical Center for Treatment and Prophylaxis of AIDS and Infectious Diseases, Samara, Russia; [9]Centro Médico Maffei & Investigación Clínica Aplicada, Buenos Aires, Argentina; [10]ViiV Healthcare, Durham, NC, USA; [11]GSK, Collegeville, PA, USA; [12]GSK, Brentford, UK; [13]GSK, Bangalore, India

19th European AIDS Conference; October 18-21, 2023; Warsaw, Poland

Presenter Disclosure Information

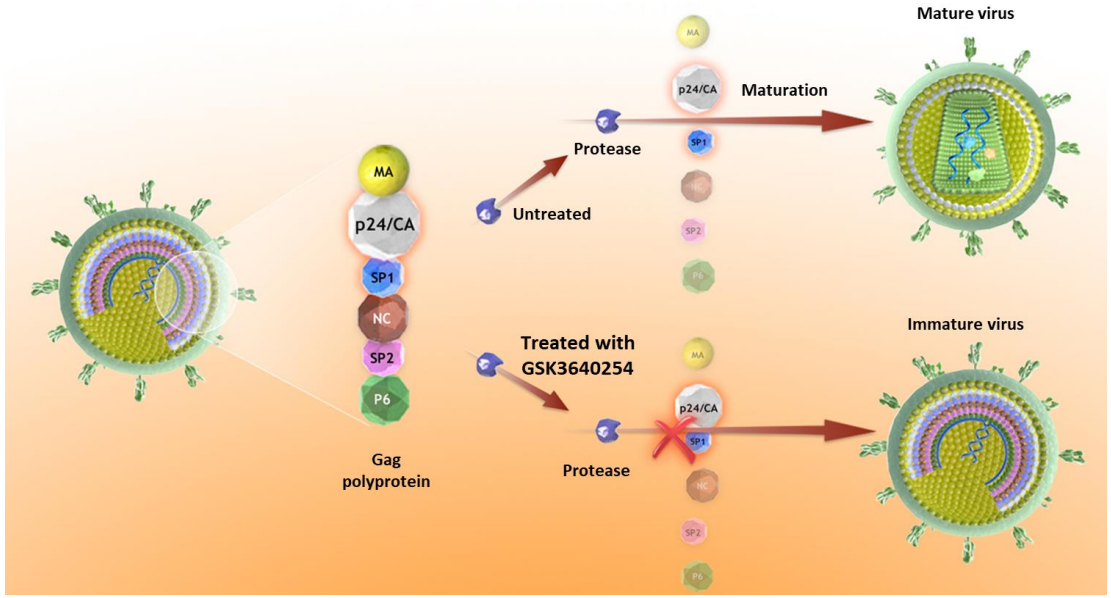
Samit R. Joshi

discloses the following pertaining to this presentation:

Employee: ViiV Healthcare

Introduction

- Antiretroviral therapy can be associated with drug resistance[1] and toxicities[2]; thus, there remains a need for antiretrovirals with novel mechanisms of action for people living with HIV-1
- Maturation inhibitors are an investigational class of antiretrovirals that target the last steps of the HIV-1 life cycle[3]
- GSK3640254 (GSK'254) is a maturation inhibitor with a unique mechanism of action that blocks the final protease cleavage event between the capsid and spacer 1 regions and has demonstrated broad-spectrum inhibition across various HIV-1 subtypes[4]
- In a proof-of-concept study, GSK'254 demonstrated a 2-log viral load reduction in treatment-naive adults with HIV-1 when provided as monotherapy[5]
- Here, we present efficacy and safety data of GSK'254 + 2 NRTIs in treatment-naive adults with HIV-1 in the phase 2b DOMINO study

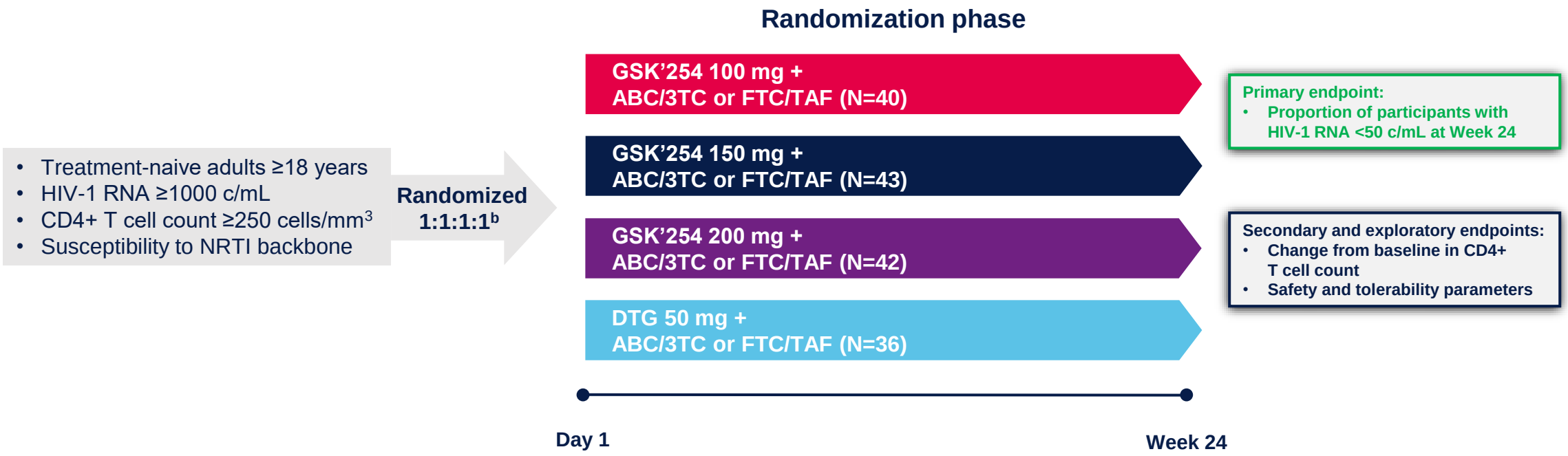


Lataillade et al. CROI 2015; Seattle, WA. Slides 114LB.

1. Arts and Hazuda. *Cold Spring Harb Perspect Med*. 2012;2:a007161. **2.** Morales-Ramirez et al. *PLoS One*. 2018;13:e0205368. **3.** Wang et al. *Acta Pharm Sin B*. 2015;5:493-499. **4.** Joshi et al. *Pharmacol Res Perspect*. 2020;8:e00671. **5.** Spinner et al. *Clin Infect Dis*. 2022;75:786-794.

Study Design and Endpoints

- DOMINO was a partially blinded, active-controlled, phase 2b trial in which treatment-naive participants were randomized to receive once-daily oral GSK'254 100, 150, or 200 mg (blinded dose) with a low-fat meal[a] or open-label DTG, all with 2 open-label NRTIs



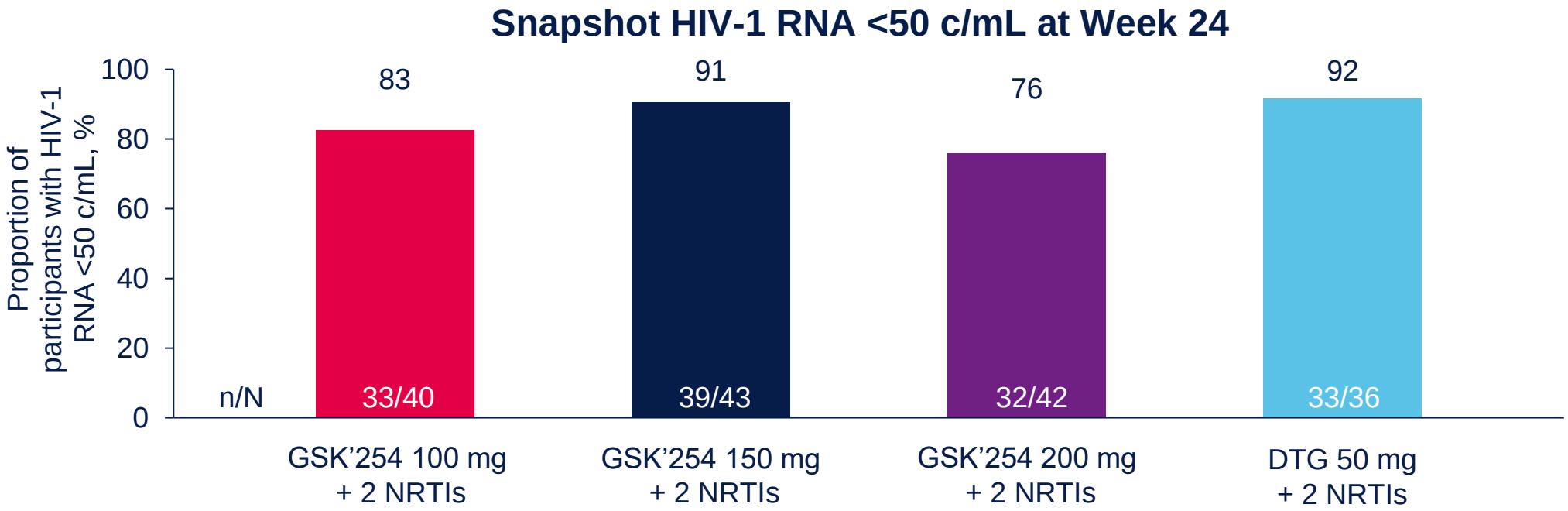
[a]Included but not limited to 400-500 calories, with 25% of calories from fat. [b]Stratified by screening plasma HIV-1 RNA and investigator's choice of dual NRTI background therapy.

Baseline Characteristics

Parameter	GSK'254 100 mg + 2 NRTIs (N=40)	GSK'254 150 mg + 2 NRTIs (N=43)	GSK'254 200 mg + 2 NRTIs (N=42)	DTG 50 mg + 2 NRTIs (N=36)
Age, median (range), y	32 (23-45)	38 (20-65)	30 (20-55)	35 (20-61)
Sex, n (%)				
Female	7 (18)	9 (21)	12 (29)	10 (28)
Race, n (%)[a]				
White	32 (80)	31 (72)	32 (76)	29 (81)
Black/African American	6 (15)	8 (19)	6 (14)	6 (17)
Asian	0	2 (5)	2 (5)	1 (3)
Other races[b]	2 (5)	2 (5)	1 (2)	0
Ethnicity, n (%)[a]				
Hispanic/Latin American	18 (45)	14 (33)	14 (33)	11 (31)
BMI, median (range), kg/m^2	25.0 (18.6-56.4)	25.3 (18.7-36.1)	25.8 (18.5-49.2)	23.8 (18.0-52.1)
HIV-1 RNA, mean (SD), log_{10} c/mL	4.35 (0.57)	4.35 (0.67)	4.17 (0.65)	4.25 (0.68)
≥100,000 c/mL, n (%)	3 (8)	7 (16)	4 (10)	6 (17)
CD4+ T cell count, median (range), $cells/mm^3$	458 (193-967)	473 (266-1177)	420 (179-972)	472 (35-1193)
Background dual NRTI				
ABC/3TC	6 (15)	7 (16)	6 (14)	6 (17)
TAF/FTC	34 (85)	36 (84)	36 (86)	30 (83)

BMI, body mass index.
[a]1 participant in the GSK'254 200 mg + 2 NRTIs group had missing data. [b]Included American Indian or Alaska Native (n=4) and individuals with multiple races (n=1).

Results: Week 24 Efficacy



- GSK'254 + 2 NRTIs demonstrated generally high and comparable efficacy to DTG + 2 NRTIs
- Mean increases from baseline to Week 24 in CD4+ T cell count were observed across the GSK'254 + 2 NRTIs groups (129.3 to 241.3 cells/mm^3) and the DTG + 2 NRTIs group (198.5 cells/mm^3)

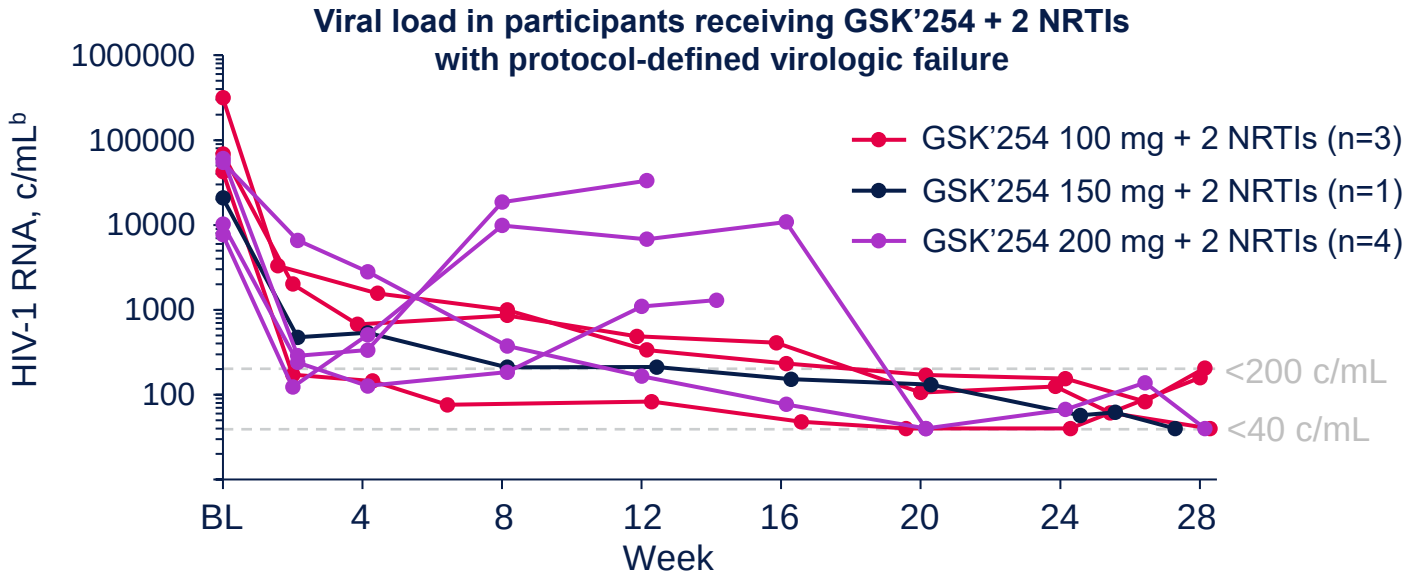
Results: Week 24 Efficacy (cont)

FDA Snapshot outcome, n (%)	GSK'254 100 mg + 2 NRTIs (N=40)	GSK'254 150 mg + 2 NRTIs (N=43)	GSK'254 200 mg + 2 NRTIs (N=42)	DTG 50 mg + 2 NRTIs (N=36)
HIV-1 RNA <50 c/mL	33 (83)	39 (91)	32 (76)	33 (92)
HIV-1 RNA ≥50 c/mL	6 (15)[a]	0	6 (14)[b]	1 (3)
Data in window and HIV-1 RNA ≥50 c/mL	5 (13)	0	2 (5)	1 (3)
Discontinued for other reason and HIV-1 RNA ≥50 c/mL[c]	1 (3)	0	4 (10)	0
No virologic data	1 (3)	4 (9)	4 (10)	2 (6)
Discontinued study because of adverse event or death	1 (3)	3 (7)	3 (7)	1 (3)
Discontinued study for other reasons[d]	0	1 (2)	1 (2)	1 (3)

[a]3 of 6 participants did not meet protocol-defined virologic failure criteria by Week 24 and achieved virologic suppression after Week 24. 3 of 6 participants had baseline HIV-1 RNA ≥100,000 c/mL; of these participants, 1 met protocol-defined virologic failure criteria and was discontinued from the study (HIV-1 RNA 83 c/mL at confirmed virologic failure) and 2 participants had blips at Week 28 but were undetectable at Week 24 and after Week 28. [b]2 of 6 participants did not meet protocol-defined virologic failure criteria by Week 24 and achieved virologic suppression after Week 24. [c]Reasons for discontinuation included protocol deviation (n=1; GSK'254 100 mg), protocol-defined virologic failure criteria met (n=3, GSK'254 200 mg), and withdrawal by participants (n=1; GSK'254 200 mg). [d]Reasons for discontinuation included exclusion criteria met (GSK'254 150 mg), physician decision (GSK'254 200 mg), and liver chemistry stopping criteria (DTG).

Protocol-Defined Virologic Failure

- Protocol-defined virologic failure[a] occurred in 8 participants receiving GSK'254 + 2 NRTIs (100 mg, n=3 [8%]; 150 mg, n=1 [2%]; 200 mg, n=4 [10%]) and 1 (3%) receiving DTG + 2 NRTIs
  - 7 of 9 participants with protocol-defined virologic failure met criteria at or before the Week 24 visit
- 4 of 9 participants with protocol-defined virologic failure had HIV-1 RNA <200 c/mL



- No treatment-emergent resistance was detected at protocol-defined virologic failure or before Week 24 across all groups[c]

[a]Protocol-defined virologic failure criteria included: decrease from baseline of HIV-1 RNA <1.0 $\log_{10}$ by Week 12; confirmed HIV-1 RNA ≥200 c/mL at or after Week 24; HIV-1 RNA ≥50 c/mL on repeat testing at Week 24 and before Week 28; confirmed HIV-1 RNA ≥200 c/mL after confirmed consecutive plasma HIV-1 RNA <50 c/mL. [b]All plot points at 40 c/mL indicate a value of <40 c/mL. [c]4 of 5 participants had results from resistance tests; the assays failed for 1 participant.

Results: Week 24 Safety

- Overall AEs were similar across GSK’254 + 2 NRTIs groups and comparable to the DTG + 2 NRTIs group
- Drug-related AEs, including those leading to withdrawal, were highest in the GSK’254 150 mg + 2 NRTIs and GSK’254 200 mg + 2 NRTIs groups
- There was no significant increase in risk observed for any common AE[a] in any GSK’254 group relative to the DTG group

AEs in safety population, n (%)	GSK’254 100 mg + 2 NRTIs (N=40)	GSK’254 150 mg + 2 NRTIs (N=43)	GSK’254 200 mg + 2 NRTIs (N=42)	DTG 50 mg + 2 NRTIs (N=36)
Any AE	35 (88)	38 (88)	37 (88)	28 (78)
Occurring in ≥10% of any group				
COVID-19	8 (20)	10 (23)	6 (14)	10 (28)
Diarrhea	5 (13)	6 (14)	5 (12)	6 (17)
Headache	4 (10)	3 (7)	7 (17)	3 (8)
Nausea	2 (5)	5 (12)	3 (7)	1 (3)
Syphilis	2 (5)	1 (2)	3 (7)	4 (11)
Upper respiratory tract infection	4 (10)	1 (2)	3 (7)	0
Grade 2-5 AEs	21 (53)	20 (47)	21 (50)	13 (36)
Drug-related AEs	5 (13)	13 (30)	13 (31)	7 (19)
Serious AEs[b]	2 (5)	4 (9)	2 (5)	2 (6)
Drug-related serious AE[c]	0	1 (2)	1 (2)	0
AEs leading to withdrawal	2 (5)	3 (7)	4 (10)	2 (6)
Drug-related AEs leading to withdrawal	0	2 (5)[d]	4 (10)[e]	1 (3)[f]

AE, adverse event.
[a]Relative risk comparisons of AEs occurring in ≥2% of participants in each group; significance was determined by a 95% confidence interval that did not overlap with 1. [b]No fatal serious AEs were reported. [c]There were 2 drug-related serious AEs: 1 of allergic dermatitis in the GSK’254 150 mg + 2 NRTIs group and 1 of pancreatitis in the GSK’254 200 mg + 2 NRTIs group; both led to study discontinuation. [d]Allergic dermatitis (n=2). [e]Mood alteration (n=1); maculopapular rash (n=1); pancreatitis (n=1); diarrhea, heartburn, rash, stomach cramps, and loss of appetite (n=1). [f]Pruritus and exanthema (n=1).

Conclusions

- The maturation inhibitor GSK’254 demonstrated generally comparable efficacy and safety/tolerability to DTG on a backbone of 2 NRTIs without treatment-emergent resistance
- Ultimately, ViiV Healthcare determined that the intended phase 3 fixed-dose combination of GSK’254-containing daily oral regimen would not be differentiated enough from existing 2-drug daily oral regimens; thus, GSK’254 was not advanced into phase 3
- However, the DOMINO data support further investigation of the next maturation inhibitor, GSK3739937, which has potential to be used as a partner agent in a long-acting regimen[1] and has recently started a phase 2a proof-of-concept study (NCT06061081)

1. Benn et al. *Pharmacol Res Perspect*. 2023;11:e01093.

Acknowledgments

- This study was funded by ViiV Healthcare
- The authors thank the study participants, investigators, and site staff who participated in the study
- 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

Presenting author: Samit R. Joshi; samit.r.joshi@viivhealthcare.com

Disclaimer

This content was acquired following an unsolicited medical information enquiry by a healthcare professional. Always consult the product information for your country, before prescribing a ViiV medicine. ViiV does not recommend the use of our medicines outside the terms of their licence. In some cases, the scientific Information requested and downloaded may relate to the use of our medicine(s) outside of their license.