Efficacy and Safety of the HIV-1 Maturation Inhibitor GSK3640254 + Dolutegravir as a 2-Drug Regimen in Treatment-Naive Adults: 24-Week Results From the Phase IIb DYNAMIC Study

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Speaker Disclosures

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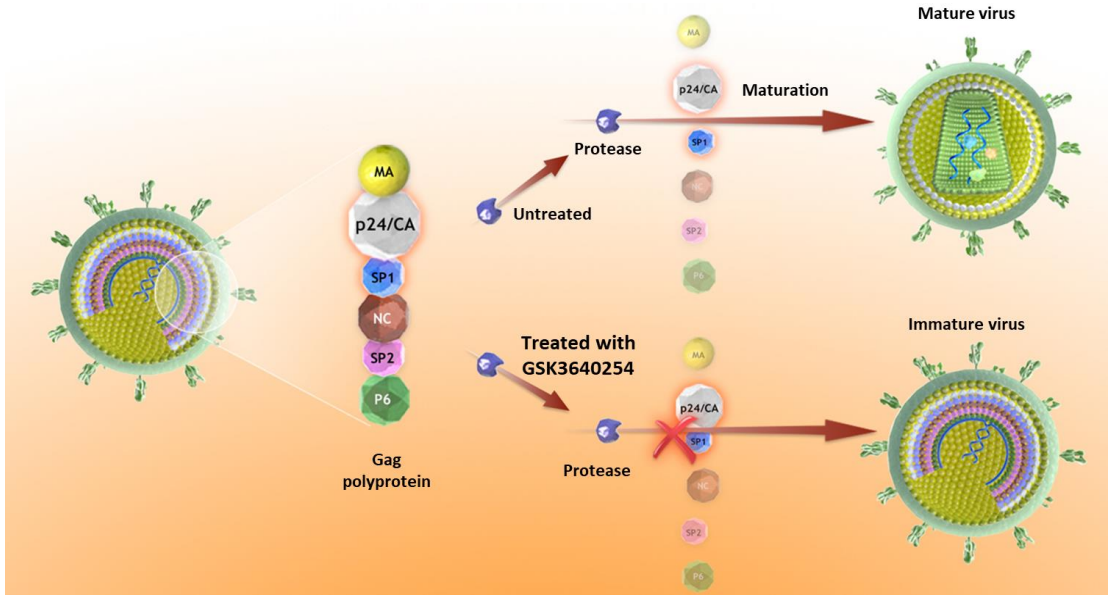
discloses the following pertaining to this presentation:

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 + DTG in treatment-naive adults with HIV-1 in the phase 2b DYNAMIC study

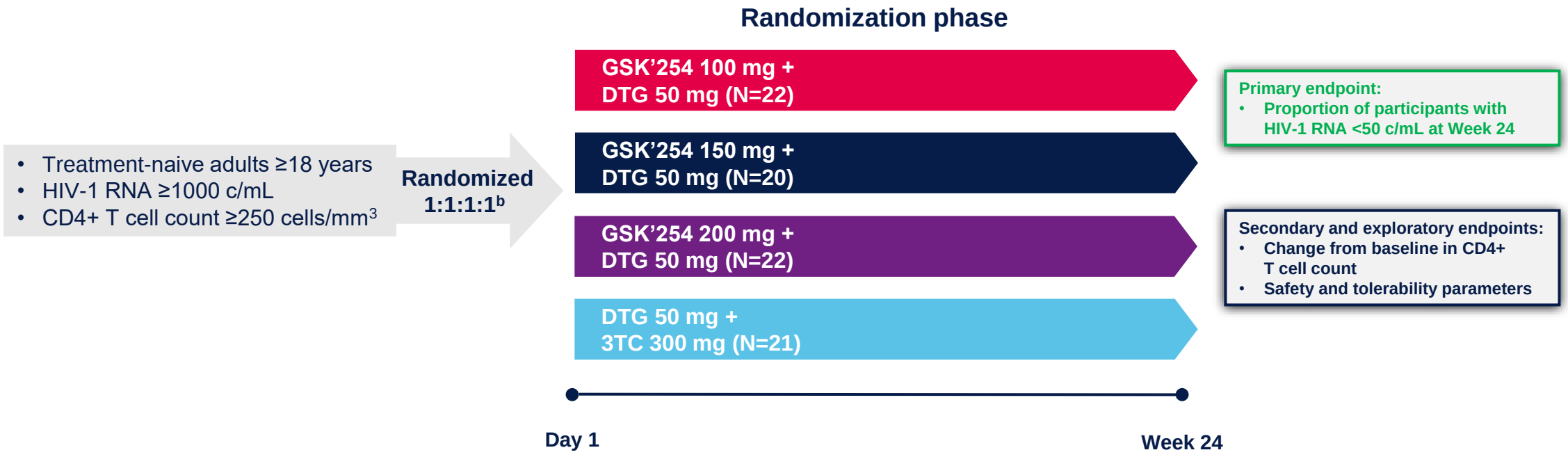


Lataillade et al. CROI 2015; Seattle, WA. Slides 114LB.

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

- DYNAMIC was a double-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) plus open-label DTG or open-label DTG plus 3TC
  - All treatments were administered with a low-fat meal[a]



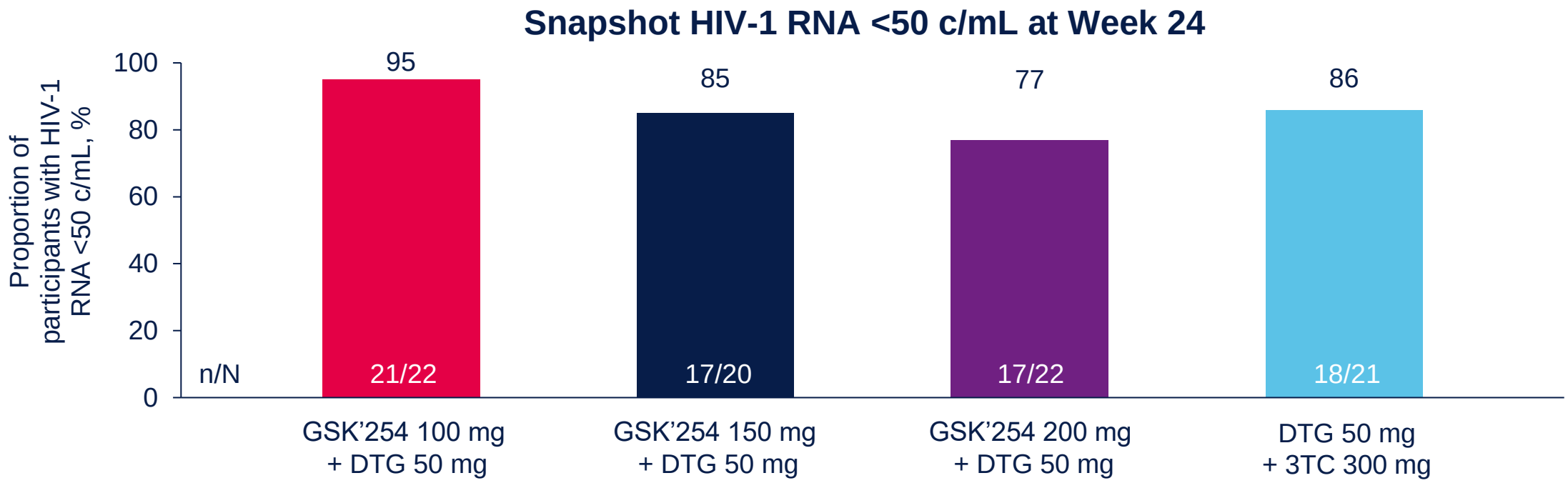
[a]Included but not limited to 400-500 calories, with 25% of calories from fat. [b]Stratified by screening plasma HIV-1 RNA.

Baseline Characteristics

Parameter	GSK'254 100 mg + DTG 50 mg (N=22)	GSK'254 150 mg + DTG 50 mg (N=20)	GSK'254 200 mg + DTG 50 mg (N=22)	DTG 50 mg + 3TC 300 mg (N=21)
Age, median (range), y	34 (23-56)	38 (21-59)	32 (18-50)	30 (20-53)
Sex, n (%)				
Female	3 (14)	4 (20)	5 (23)	3 (14)
Race, n (%)				
White	18 (82)	14 (70)	16 (73)	14 (67)
Black/African American	3 (14)	4 (20)	3 (14)	3 (14)
Asian	0	0	0	1 (5)
Mixed race	0	1 (5)	1 (5)	0
Unknown	1 (5)	1 (5)	2 (9)	3 (14)
Ethnicity, n (%)				
Hispanic/Latin American	15 (68)	8 (40)	11 (50)	12 (57)
BMI, median (range), kg/m^2	27.1 (19.0-41.2)	25.8 (18.6-38.9)	25.5 (19.6-35.8)	24.3 (20.2-33.8)
HIV-1 RNA, mean (SD), log_{10} c/mL	4.61 (0.53)	4.45 (0.59)	4.54 (0.42)	4.18 (0.59)
≥100,000 c/mL, n (%)	5 (23)	3 (15)	4 (18)	2 (10)
CD4+ T cell count, median (range), $cells/mm^3$	405 (223-733)	408 (280-843)	483 (247-988)	453 (245-928)

BMI, body mass index.

Results: Week 24 Efficacy



- Across treatment groups, GSK'254 + DTG demonstrated generally high rates of virologic suppression and comparable efficacy to DTG + 3TC
- Mean increases from baseline to Week 24 in CD4+ T cell count were observed in the GSK'254 + DTG groups (200.6 to 317.7 cells/mm^3) and the DTG + 3TC group (139.5 cells/mm^3)

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Results: Week 24 Efficacy (cont)

FDA Snapshot outcome, n (%)	GSK'254 100 mg + DTG 50 mg (N=22)	GSK'254 150 mg + DTG 50 mg (N=20)	GSK'254 200 mg + DTG 50 mg (N=22)	DTG 50 mg + 3TC 300 mg (N=21)
HIV-1 RNA <50 c/mL	21 (95)	17 (85)	17 (77)	18 (86)
HIV-1 RNA ≥50 c/mL	0	3 (15)	5 (23)	2 (10)
Data in window and HIV-1 RNA ≥50 c/mL	0	2 (10)	5 (23)	2 (10)
Discontinued for other reason and HIV-1 RNA ≥50 c/mL	0	1 (5)[a]	0	0
No virologic data	1 (5)	0	0	1 (5)
Discontinued study because of adverse event or death	1 (5)	0	0	1 (5)

- Protocol-defined virologic failure[b] occurred in 1 participant receiving GSK'254 200 mg + DTG and 1 receiving DTG + 3TC[c]
- No treatment-emergent resistance was detected[d]

[a]Participant withdrew due to protocol deviation at Day 100 (dosing non-compliance) with no adverse events reported. [b]Protocol-defined virologic 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. [c]Participant was diagnosed with a concomitant monkeypox viral infection. [d]Resistance testing data were not available for the participant in the GSK'254 200 mg group.

Results: Week 24 Safety

- Overall AEs were similar across GSK'254 treatment groups and comparable to the DTG group
- There were no drug-related serious AEs, and drug-related AEs leading to withdrawal were rare
- There was no significant increase in risk observed for any common AE[a] in any GSK'254 + DTG group relative to the DTG + 3TC group
  - Participants receiving the 150 and 200 mg doses of GSK'254 + DTG had a numerically higher number of AEs with diarrhea compared with DTG + 3TC

AEs in safety population, n (%)	GSK'254 100 mg + DTG 50 mg (N=22)	GSK'254 150 mg + DTG 50 mg (N=20)	GSK'254 200 mg + DTG 50 mg (N=22)	DTG 50 mg + 3TC 300 mg (N=21)
Any AE	17 (77)	15 (75)	20 (91)	15 (71)
Occurring in ≥10% of any group				
COVID-19	3 (14)	2 (10)	4 (18)	3 (14)
Diarrhea	1 (5)	4 (20)	5 (23)	1 (5)
Headache	2 (9)	3 (15)	3 (14)	2 (10)
Upper respiratory tract infection	2 (9)	1 (5)	2 (9)	3 (14)
Nasopharyngitis	1 (5)	1 (5)	3 (14)	2 (10)
Influenza-like illness	1 (5)	2 (10)	1 (5)	1 (5)
Nausea	1 (5)	1 (5)	1 (5)	2 (10)
Pyrexia	1 (5)	3 (15)	0	0
Arthralgia	0	2 (10)	1 (5)	0
Back pain	0	2 (10)	0	1 (5)
Dizziness	0	2 (10)	0	1 (5)
Toothache	0	2 (10)	0	1 (5)
Abdominal pain	0	2 (10)	0	0
Influenza	0	0	0	2 (10)
Grade 2-5 AEs	8 (36)	7 (35)	11 (50)	7 (33)
Drug-related AEs	4 (18)	4 (20)	8 (36)	3 (14)
Serious AEs[b]	2 (9)	0	0	1 (5)
AEs leading to withdrawal	1 (5)	0	1 (5)	0
Drug-related AEs leading to withdrawal	1 (5)[c]	0	0	0

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 serious adverse events were related to treatment and none were fatal. [c]Grade 2 hypertensive nephropathy that resolved with sequelae.

Joshi et al. EACS 2023; Warsaw, Poland. Slides RA2.O2.

Conclusions

- GSK’254 + DTG demonstrated generally comparable efficacy and safety/tolerability to DTG + 3TC without treatment-emergent resistance
- Ultimately, ViiV Healthcare determined that the intended phase 3 FDC of GSK’254 + DTG would not be differentiated enough from existing 2-drug daily oral regimens; thus, GSK’254 + DTG FDC was not advanced into phase 3
- This study represents the first time a 2-drug regimen with a maturation inhibitor has been evaluated and supports further investigation of maturation inhibitors for the treatment of HIV-1
- The maturation inhibitor GSK3739937, which has shown potential to be used as a partner agent in a complete long-acting regimen,[1] has recently started a phase 2a proof-of-concept study (NCT06061081)

FDC, fixed-dose combination.

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

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