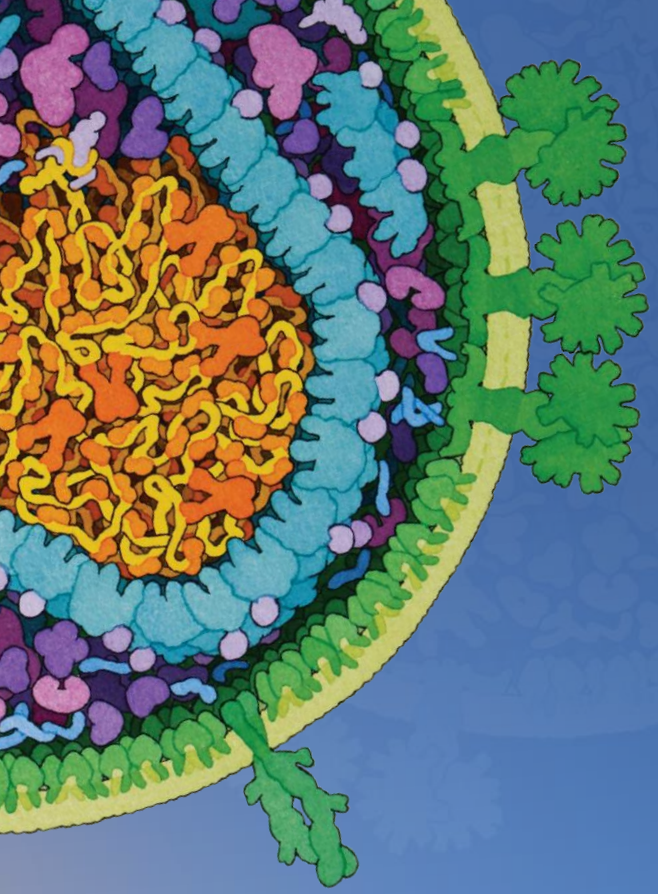

ORAL ABSTRACT

PHASE IIA PROOF-OF-CONCEPT TRIAL OF NEXT-GENERATION MATURATION INHIBITOR GSK3640254

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Introduction

- Drug resistance and toxicities with HIV-1 regimens can result in treatment failure, necessitating the development of antiretroviral therapy (ART) agents with new mechanisms of action
- GSK3640254 (GSK'254) is a novel, next-generation HIV-1 maturation inhibitor that has demonstrated inhibition across all HIV-1 subtypes[1]
- In phase I clinical trials in healthy participants, GSK'254 was well tolerated and displayed pharmacokinetics (PK) to support unboosted, once-daily therapy[2]
- We present the final results from a phase IIa proof-of-concept study evaluating the antiviral effect, PK, safety, and tolerability of once-daily GSK'254 administered with a moderate-fat meal in treatment-naive adults with HIV-1 infection

1. Jeffrey et al. CROI 2021; Virtual. Slides 1824. **2.** Joshi et al. *Pharmacol Res Perspect*. 2020;8:e00671.

GSK’254 Proposed Mechanism of Action[1,2]

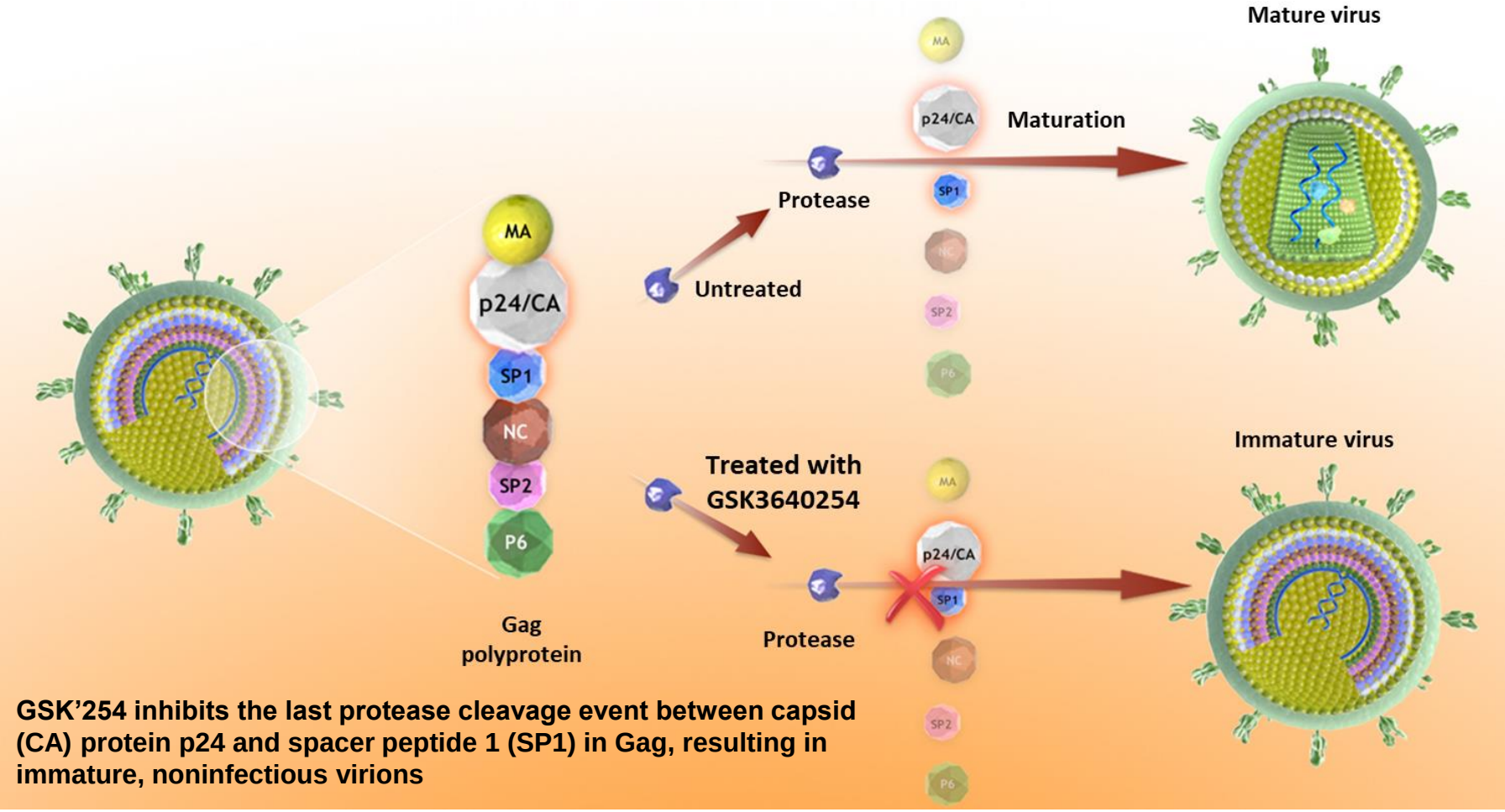
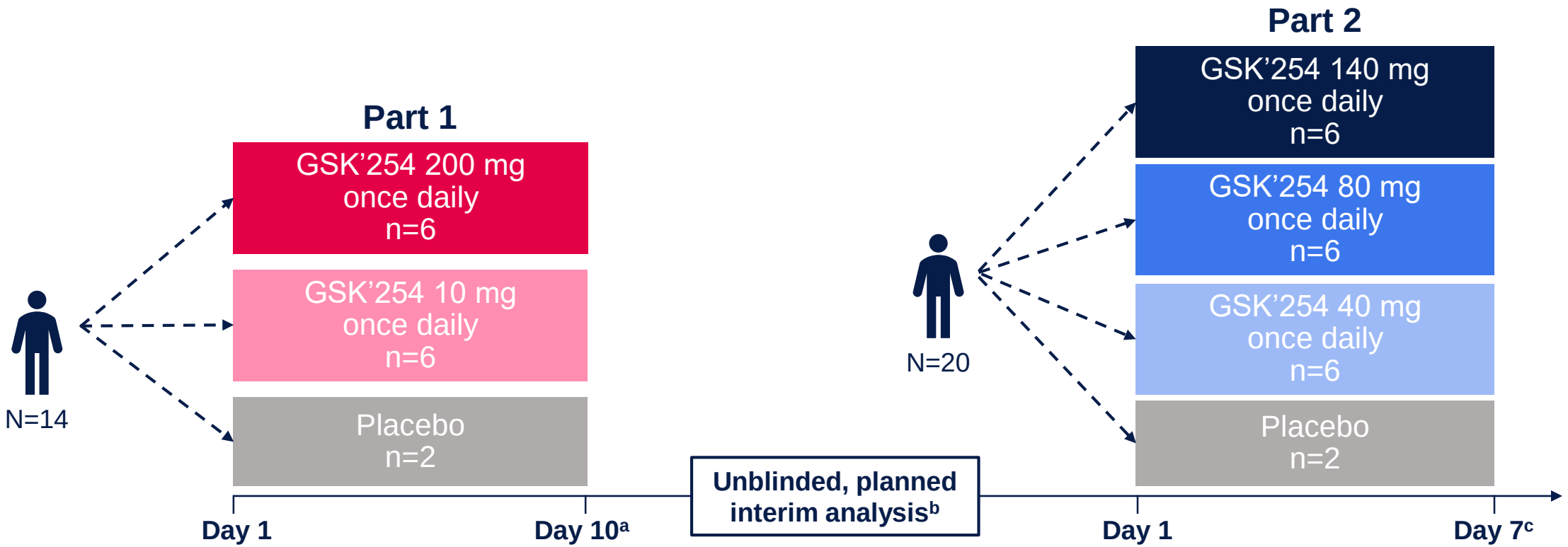


Figure adapted from Lataillade et al. Conceptualization of HIV-1 maturation inhibition, and design of the mode of action of GSK3532795. In: 22nd CROI; February 22-26, 2015; Seattle, WA. Oral presentation 114LB.

1. Adamson et al. *Expert Opin Ther Targets*. 2009;13:895-908. **2.** Hwang et al. *Clin Infect Dis*. 2017;65:442-452.

Study Design: Double-blind (Sponsor-Unblinded), Randomized, Placebo-Controlled, Adaptive Study in ART-Naive Adults



Primary endpoint: maximum change from Day 1 in plasma HIV-1 RNA during parts 1 and 2

[a]Participants attended 1 follow-up visit during Days 11-17 and started combination ART after the final follow-up visit during Days 18-24.

[b]To determine whether to proceed to part 2. Treatment-emergent resistance-associated mutations were noted in the 200-mg group in part 1. Thus, the sponsor temporarily halted the study and conducted resistance analyses. A subsequent protocol amendment decreased monotherapy from 10 to 7 days in part 2 to reduce potential for treatment-emergent resistance mutations.

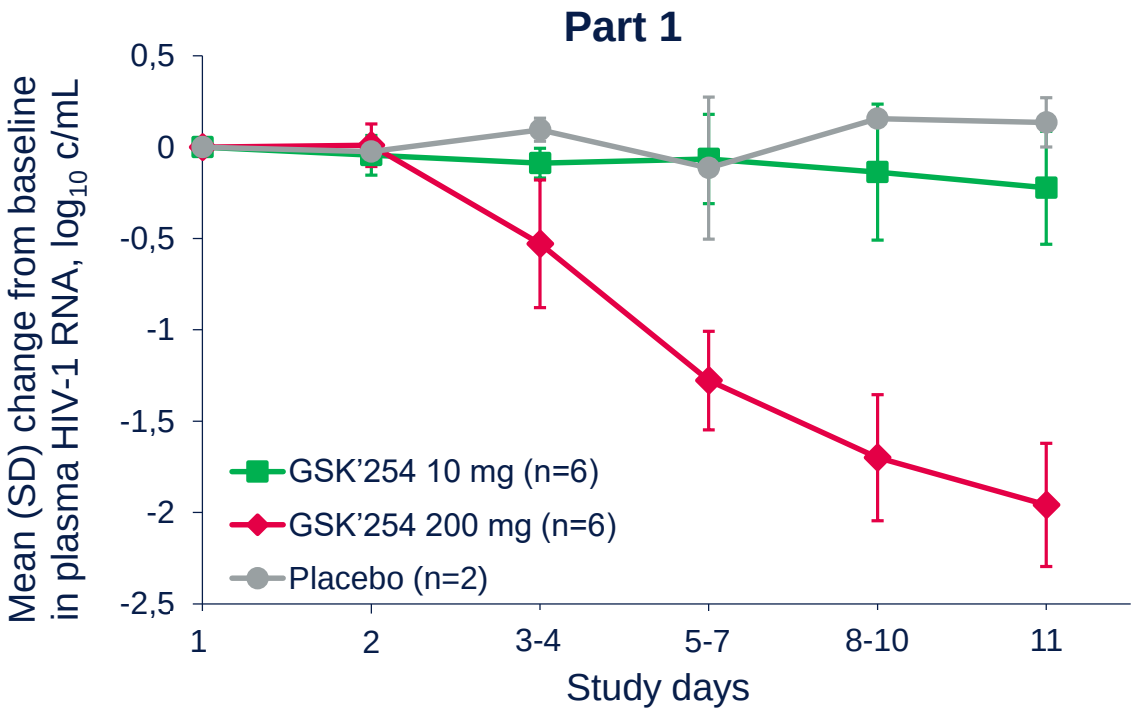
[c]Participants started combination ART at the follow-up visit on Day 8 and attended a final follow-up visit during Days 10-12.

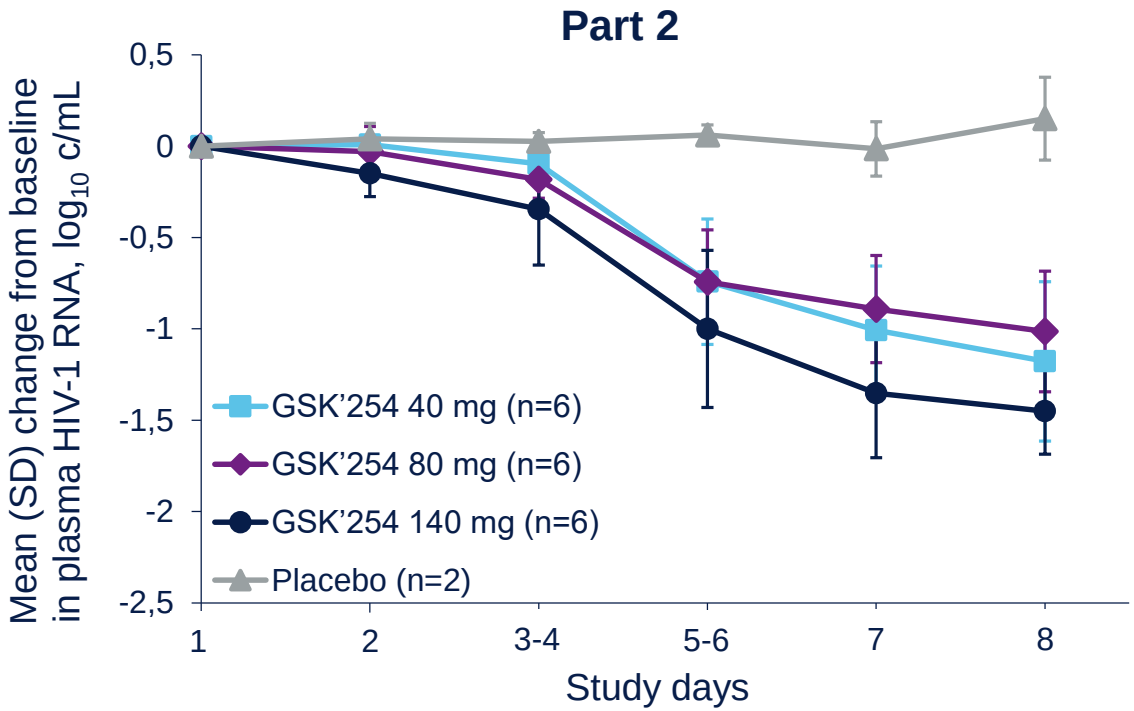
Baseline Characteristics

Parameter	GSK'254 10 mg (n=6)	GSK'254 40 mg (n=6)	GSK'254 80 mg (n=6)	GSK'254 140 mg (n=6)	GSK'254 200 mg (n=6)	Placebo (n=4)	Total (N=34)
Age, mean (SD), y[a]	32.7 (8.3)	27.7 (6.9)	32.8 (6.2)	33.2 (8.2)	29.3 (3.9)	36.5 (9.3)	31.8 (7.2)
Sex, n (%)							
Female	0	1 (17)	0	1 (17)	0	0	2 (6)
Male	6 (100)	5 (83)	6 (100)	5 (83)	6 (100)	4 (100)	32 (94)
Body mass index, mean (SD), kg/m^2	25.3 (3.7)	23.9 (4.3)	24.8 (3.7)	23.4 (1.6)	22.6 (2.2)	23.0 (1.3)	23.9 (3.0)
Race, n (%)							
White/Caucasian/European heritage	2 (33)	5 (83)	4 (67)	5 (83)	5 (83)	3 (75)	24 (71)
Black/African American	0	1 (17)	2 (33)	1 (17)	0	0	4 (12)
Other	4 (67)[b]	0	0	0	1 (17)[c]	1 (25)[d]	6 (18)
Plasma HIV-1 RNA, mean (SD), log_{10} c/mL	4.19 (0.311)	4.67 (0.233)	4.43 (0.510)	4.53 (0.577)	4.82 (0.476)	4.25 (0.417)[e] 4.25 (0.417)[f]	4.47 (0.489)[g] 4.57 (0.592)[h]

[a]Age was imputed when full date of birth was not provided. [b]American Indian/Alaska native (n=2), Asian/Southeast Asian heritage (n=1), and multiple races (n=1). [c]Multiple races (n=1). [d]American Indian/Alaska native (n=1). [e]Placebo group in part 1. [f]Placebo group in part 2. [g]Total population in part 1 (N=14). [h]Total population in part 2 (N=20).

Plasma HIV-1 RNA Decreased With All GSK'254 Doses in Parts 1 and 2



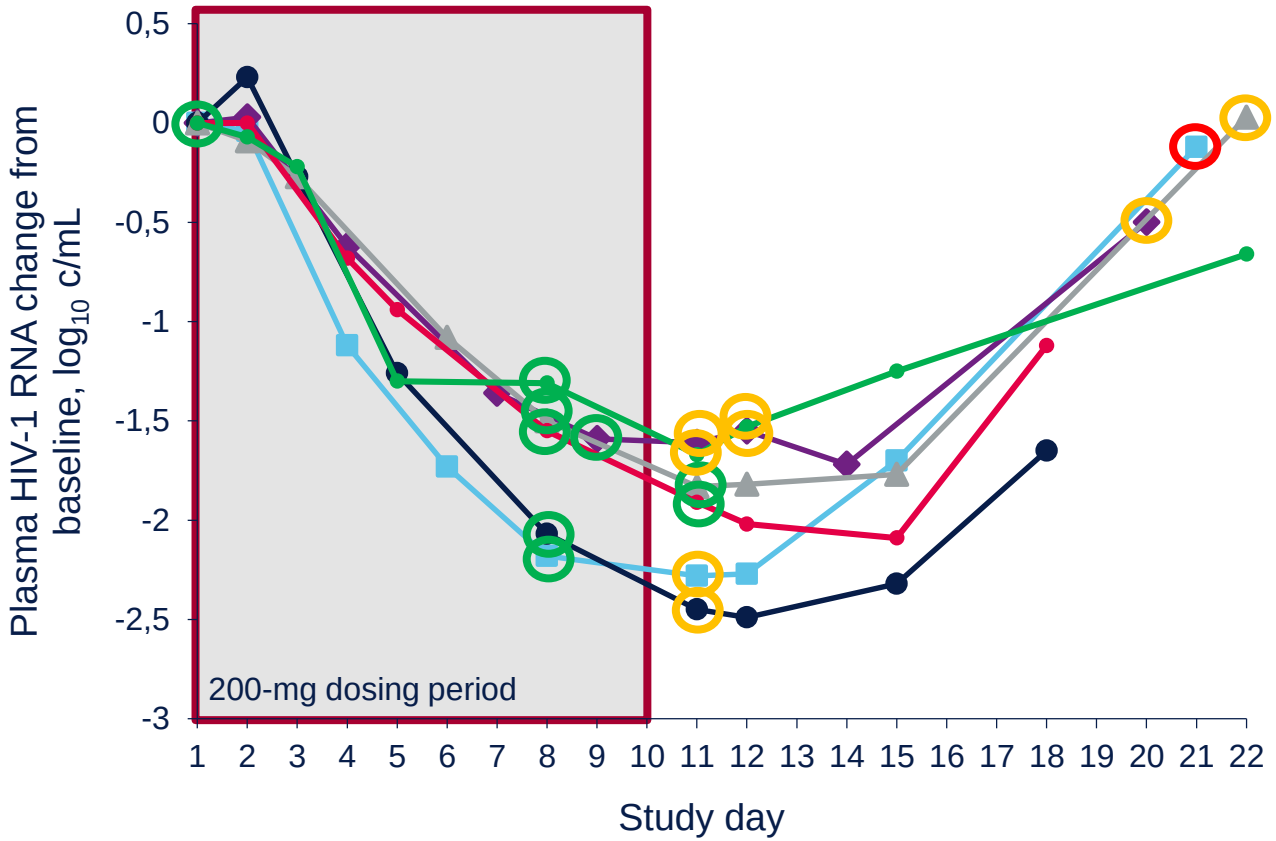


Plasma HIV-1 RNA change from baseline, mean (SD), log_{10} c/mL	Part 1 (Day 11) GSK'254 10 mg (n=6)	Part 1 (Day 11) GSK'254 200 mg (n=6)	Part 1 (Day 11) Placebo (n=2)	Part 2 (Day 8) GSK'254 40 mg (n=6)	Part 2 (Day 8) GSK'254 80 mg (n=6)	Part 2 (Day 8) GSK'254 140 mg (n=6)	Part 2 (Day 8) Placebo (n=2)
Primary endpoint	−0.22 (0.309)	−1.96 (0.337)	0.14 (0.134)	−1.18 (0.436)	−1.02 (0.330)	−1.45 (0.235)	0.15 (0.226)
Maximum change	−0.36 (0.252)	−2.01 (0.329)	−0.21 (0.262)	−1.18 (0.436)	−1.02 (0.330)	−1.49 (0.267)	−0.03 (0.127)

Resistance Analysis

- In part 1, 4 of 6 participants in the 200-mg GSK’254 group developed the resistance-associated mutation A364A/V at Day 11 after 10 days of monotherapy
  - 1 in 4 participants with resistance-associated mutations developed phenotypic resistance (132-fold change from baseline in half-maximal inhibitory concentration)
  - No genotypic or phenotypic resistance was observed in the 10-mg group
- A protocol amendment modified the duration of monotherapy from 10 to 7 days in part 2 to decrease the potential for treatment-emergent resistance-associated mutations
- No genotypic or phenotypic resistance was observed at any GSK’254 dose in part 2

200-mg group HIV-1 gag genotyping results: Day 8 to end of study



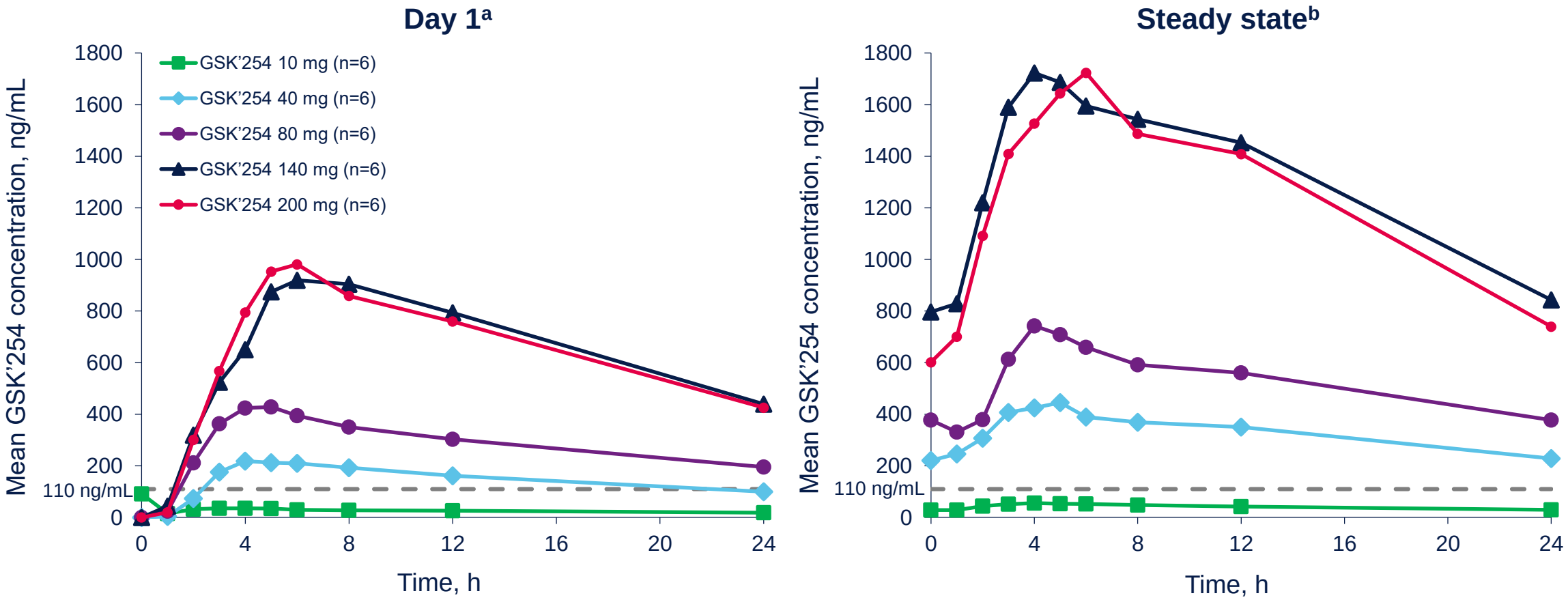
A364V: Full conversion of the mixture and loss of sensitivity to GSK’254

A364A/V: Mixed population of amino acids “A” and “V” with partial resistance to GSK’254

No resistance

Spinner et al. CROI 2021; Virtual. Slides 1975.

GSK’254 PK Results



- Mean GSK’254 concentrations were above the clinical efficacy target of 110 ng/mL[c] for the 40- to 200-mg GSK’254 doses

[a]One participant in the 10-mg group had a predose concentration that was inconsistent with the expected PK profile. One participant in the 200-mg group was excluded from PK analysis due to vomiting postdose ≤1 × tmax. [b]Steady state was measured at Days 8-9 in part 1 and Day 7 in part 2. [c]Value for which ≥95% of participants in a phase IIb study are projected to reach target trough concentrations.

Safety and Tolerability

Preferred term, n (%)[a]	GSK'254 10 mg (n=6)	GSK'254 40 mg (n=6)	GSK'254 80 mg (n=6)	GSK'254 140 mg (n=6)	GSK'254 200 mg (n=6)	Placebo (n=4)	Total (N=34)
Any adverse event (AE)	3 (50)	5 (83)	4 (67)	5 (83)	5 (83)	0	22 (65)
Headache	0	1 (17)	0	1 (17)	2 (33)	0	4 (12)
Diarrhea	1 (17)	1 (17)	0	0	1 (17)	0	3 (9)
Oropharyngeal pain	0	0	0	1 (17)	2 (33)	0	3 (9)
Abdominal pain	0	0	2 (33)	0	0	0	2 (6)
Nasopharyngitis	0	0	0	0	2 (33)	0	2 (6)
Lymphadenopathy	1 (17)	0	0	0	1 (17)	0	2 (6)
Vomiting	1 (17)	0	0	0	1 (17)	0	2 (6)
Any drug-related AE	2 (33)	2 (33)	2 (33)	1 (17)	2 (33)	0	9 (26)
Diarrhea	1 (17)	1 (17)	0	0	1 (17)	0	3 (9)
Abdominal pain	0	0	2 (33)	0	0	0	2 (6)
Vomiting	1 (17)	0	0	0	1 (17)	0	2 (6)

- All drug-related AEs were grade 1 (11 events) or grade 2 (3 events) in intensity
- Serious AEs of anal abscess (grade 1; n=1) and congestive cardiomyopathy (grade 3; n=1) were reported; not considered drug related
  - The participant from the 10-mg group who developed congestive cardiomyopathy also experienced an AE of myocarditis (grade 3; not drug related)
- No AEs led to discontinuation, and no deaths occurred

[a]Reported in >5% of participants.

Conclusions

- This phase IIa study established a GSK’254 dose–antiviral response relationship
- No safety or tolerability concerns were noted, with no AEs leading to discontinuation
- Dose-proportional PK was generally observed across the 10- to 200-mg GSK’254 dose range
- Across all doses evaluated and regardless of dosing duration, GSK’254 140- and 200-mg doses demonstrated the greatest declines in plasma HIV-1 RNA, with decreases of 1.5 and 2.0 $\log_{10}$ c/mL, respectively
- These results support the ongoing phase IIb study evaluating the safety, efficacy, and dose response of GSK’254 (100, 150, or 200 mg) in combination with 2 nucleoside reverse transcriptase inhibitors in treatment-naive adults with HIV-1[1]

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04493216. Accessed January 25, 2021.

Acknowledgments

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