Next-Generation Maturation Inhibitor GSK3640254 Showed Broad Spectrum Potency Without MI Resistance

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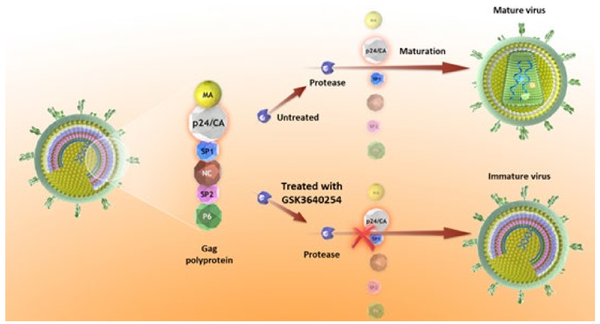
Introduction

- HIV-1 maturation inhibitors (MIs) offer a novel mechanism of action but have suffered from gag polymorphisms and decreased antiviral potency
- GSK3640254 (GSK'254) is a next-generation MI that demonstrated broad spectrum coverage of gag polymorphisms in vitro[1] (see background)
- GSK'254 + 2 nucleoside reverse transcriptase inhibitors (NRTIs) demonstrated comparable efficacy to DTG + 2 NRTIs with no treatment-emergent resistance across all doses and a comparable safety/tolerability profile in the DOMINO phase 2b dose-ranging study[2]
- HIV-1 gag/protease from Day 1 baseline and on-treatment samples were tested for sensitivity to GSK'254 and gag sequences generated to identify polymorphisms and/or treatment emergent resistance mutations

GSK'254 Mechanism of Action[3]



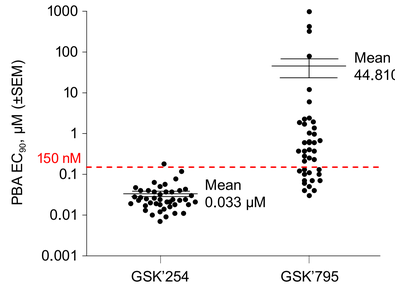
Methods

- Plasma samples were collected from all study participants at Day 1 pre-dose GSK'254 and 2 NRTI backbone
- Plasma samples were collected from any participant at suspected and confirmed protocol-defined virologic failure (PDVF) time points
- GSK'254 phenotypic data were generated at Monogram BioSciences[4] using the PhenoSense gag assay
- HIV gag genotypic data were generated at Monogram BioSciences[4] using next-generation sequencing platform
- HIV subtype based on gag sequence and a Monogram BioSciences[4] algorithm

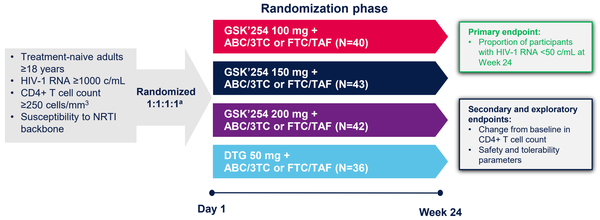
- All viruses from DOMINO participants were sensitive to GSK'254 at baseline
- No virus developed on treatment change to GSK'254 by Week 4
- No PDVF case developed resistance to GSK'254 or the NRTI backbone

Background[1]

GSK'254 demonstrated broad spectrum coverage of gag polymorphisms in vitro compared to the previous MI GSK3739937[1]



Study Design



[a]Stratified by screening plasma HIV-1 RNA and investigator's choice of dual NRTI background therapy.

Subtype Representation in the DOMINO Study

Subtype based on gag sequence						
Subtype	A1	B	C	D	F1	G
#	22	65	22	1	21	3

Note: 5 participants had discordant subtypes between Day 1 vs Week 4.

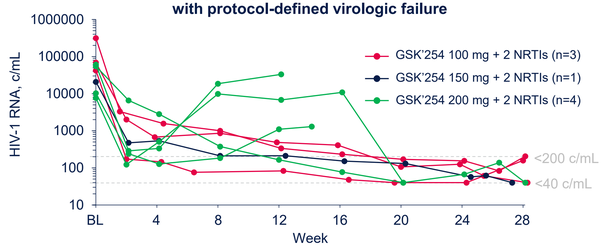
Summary of Gag Genotypes at Day 1 and Week 4

Treatment group	n	Genotype at Day 1 and Week 4 (footnotes denote minor changes from Day 1)							
		H219	R286	P289	V323	V362	A364	A366	V370
GSK'254 100 mg + 2 NRTIs (N=24)	5		R286K						
	3	H219Q	R286K						
	3	H219Q							
	1		R286K			V362I			V370A
	1				V323I				V370VTS[a]
	1		R286K		V323T				V370I
	1		R286K						V370A
	1		R286K						V370I
	1				V323V/I				
	1								V370A
	6				No polymorphisms				
GSK'254 150 mg + 2 NRTIs (N=26)	7		R286K						
	2	H219Q	R286K						
	2	H219Q							
	2	H219Q							V370A
	2		R286K						V370A
	1					V362I			
	1	H219H/Q[b]							V370V/A[c]
	1								V370Δ[d]
	1								V370A
	1	H219Q							V370V/M
	1		R286K						V370L
	1	H219Q	R286K						V370Δ
	4				No polymorphisms				
GSK'254 200 mg + 2 NRTIs (N=17)	3		R286K						
	2								V370A
	1					V362I			V370T
	1		R286K		V323I				V370A
	1	H219H/Q[e]							V370V/M[f]
	1	H219Q							
	1								V370I
	1	H219H/Q	R286K						V370A
	1	H219Q	R286K						V370A
	1	H219Q							V370A
	1	H219H/Q[e]							
	1	H219H/Q[b]							V370M
	1	H219Q							V370V/I[g]
	1				No polymorphisms				
DTG 50 mg + 2 NRTIs (N=4)	1		R286K						V370A
	1		R286K						
	1								V370A
	1					V362I			

[a]Week 4: V370ITS/VTS. [b]Week 4: Wild-type. [c]Week 4: V370A. [d]Week 4: V370T. [e]Week 4: H219Q. [f]Week 4: V370M. [g]Week 4: V370I.

Summary of Viral Loads From Participants Who Met PDVF Criteria[2]

Viral load in participants receiving GSK'254 + 2 NRTIs with protocol-defined virologic failure



PDVF Failure Criteria

- HIV-1 RNA decrease from baseline of <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

PDVF Cases Through Primary Endpoint

- PDVF occurred in 9 participants; 8 receiving GSK'254 and 1 receiving DTG
- No treatment-emergent resistance was detected in any PDVF case
- No change observed for in vitro phenotypic potency to GSK'254 or the 2 NRTI backbone

Conclusions

- All viruses from baseline were sensitive to GSK'254 (IC_{50} range 0.39-18.4 nM)
- HIV-1 subtypes from A1, B, C, D, F1, and G were represented in the study
- Various gag polymorphisms were detected in the virus from participants from the study
  - Specifically, R286K, V362I, and various V370 substitutions
- 9 participants met PDVF criteria (8 receiving GSK'254 and 1 receiving DTG)
  - No genotypic resistance to GSK'254 or the 2 NRTI backbone detected
  - No phenotypic change in IC_{50} detected to GSK'254 or the 2 NRTI backbone
  - No resistance was detected to DTG in the 1 PDVF case
- These data support further development of MIs as an anti-HIV target
  - See poster 633 in poster session G2 for information on the preclinical profile of VH-937, an MI currently in phase 2a clinical development

Acknowledgments: ViiV Healthcare would like to thank all of the study sites and the participants in DOMINO clinical trial.

References: 1. Dicker et al. *Antimicrob Agents Chemother.* 2022;66:e01876-21. **2.** Joshi et al. EACS 2023; Warsaw, Poland. Slides RA2.O1. **3.** Lataillade et al. CROI 2015; Seattle, WA. Slides 114LB. **4.** labcorp. https://monogrambio.labcorp.com/. Accessed February 16, 2024.

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