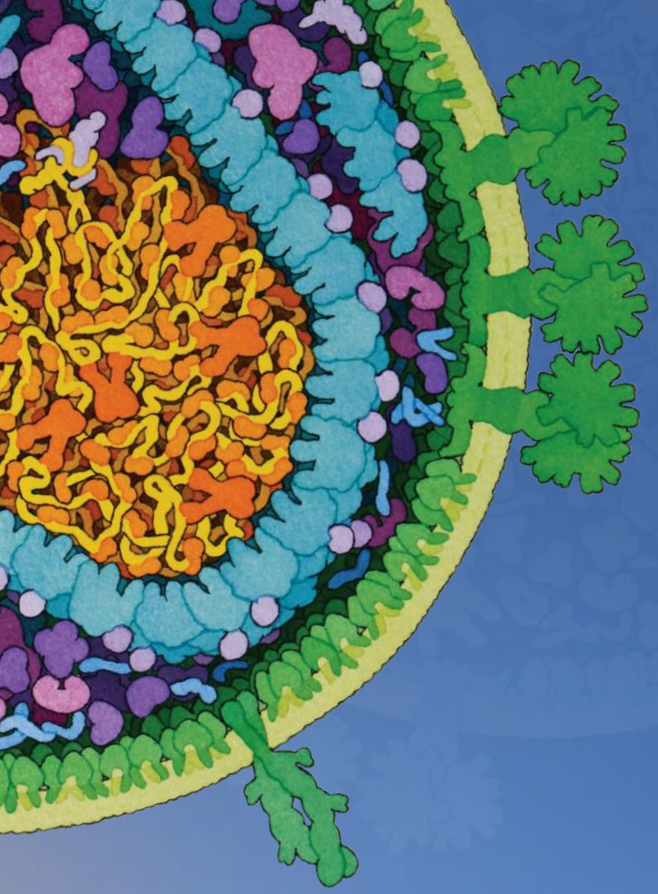

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GSK3640254 IS A NOVEL MATURATION INHIBITOR WITH AN OPTIMIZED VIROLOGY PROFILE

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Introduction

- HIV-1 maturation inhibitors work late in the replication cycle to block the cleavage of Gag p25 into p24 (capsid) and spacer peptide 1, resulting in release of noninfectious virions[1,2]
- Previous maturation inhibitors (MIs) have demonstrated clinical efficacy but encountered virologic failures in individuals infected with viruses containing key Gag polymorphisms, such as V362I and the 369-370 region of Gag[3]
- GSK3640254 (GSK'254) is a new maturation inhibitor currently under phase 2b evaluation with an optimized profile that strongly inhibits viruses containing key Gag polymorphisms[4,5]
  - A medicinal chemistry approach, coupled with a virology triage strategy focused on key Gag polymorphisms, was used to identify GSK'254
- The antiviral activity of GSK'254 against select site-directed mutants was compared with a prior maturation inhibitor, GSK3532795 (GSK'795; formerly BMS-955176)
- Broad-spectrum antiviral activity of GSK'254 was also examined against primary clinical isolates across various HIV subtypes and against recombinant viruses with *Gag* genotypes cloned from clinical isolates
- Biochemical and resistance studies were also used to confirm the mechanism of action of GSK'254

1. Adamson et al. *Expert Opin Ther Targets*. 2009;13:895-908. **2.** Hwang et al. *Clin Infect Dis*. 2017;65:442-452. **3.** Adamson et al. *Retrovirology*. 2010;7:36. **4.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04493216. Accessed February 3, 2021. **5.** Joshi et al. *Pharmacol Res Perspect*. 2020;8:e00671.

Potency of GSK'254 Against HIV With Key Gag Polymorphisms in a Single-Cycle Assay

- Compared with wild-type virus, site-directed mutant viruses with Gag changes V362I, V370A, ΔV370, or V370A/R286K were equally inhibited by GSK'254

Viral genotype	EC_{50}, μM	Fold change vs wild-type	Maximal percent inhibition, %
Wild-type	0.0023	1.0	99
V370A	0.0018	0.8	99
V370M	0.0014	0.6	98
V362I	0.0026	1.1	96
ΔV370/T371A	0.0026	1.1	99
ΔV370	0.0058	2.4	94
ΔV370A/R286K	0.0038	1.6	93
A364V	>3	>630	37

EC_{50}, concentration producing a 50% inhibitory effect.

Potency of GSK'254 Against Primary Isolates Across Various Subtypes

- The potency of GSK'254 was greater compared with GSK'795 against a panel of 19 clinical isolates, with a median EC_{50} of 3 nM (range: 1-77) vs 8 nM for GSK'795 (range: 1-1575)

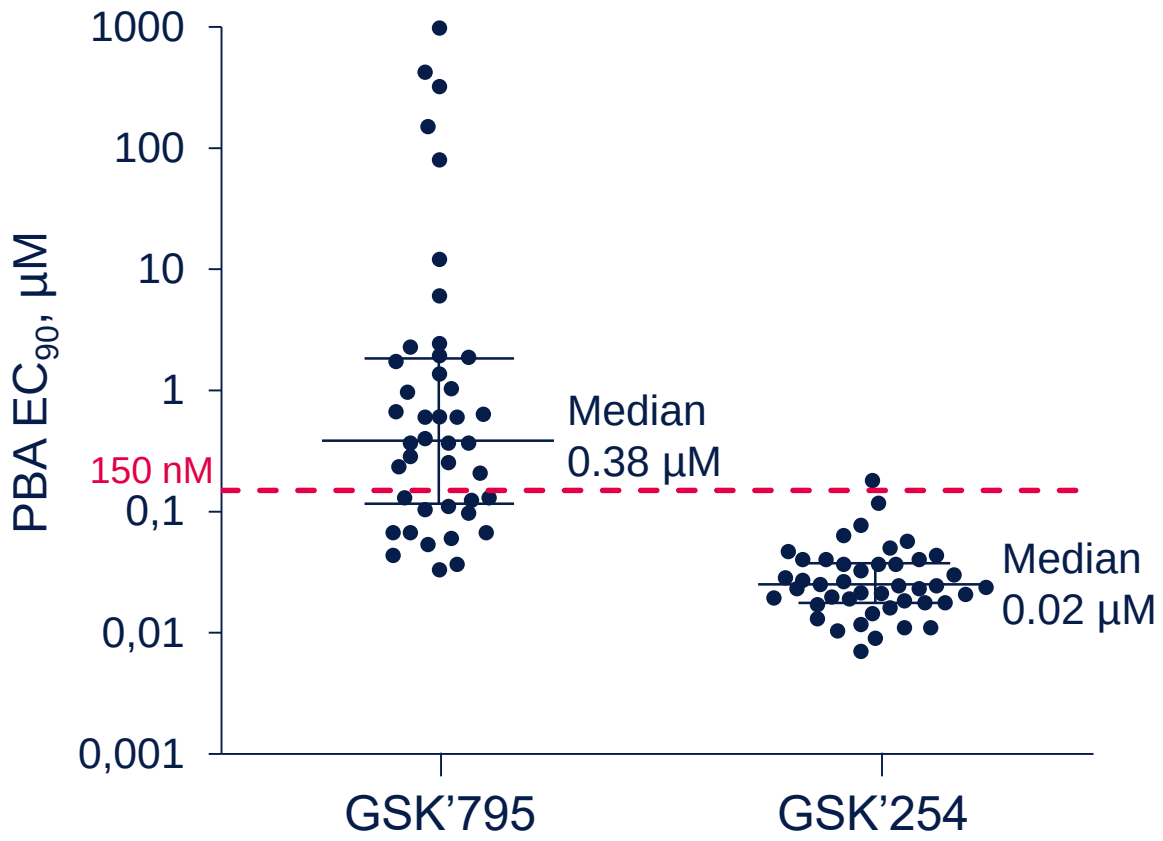
		EC_{50}, µM	
Subtype	Key Gag polymorphisms	GSK'254	GSK'795
B	V218A/V370M/N372G	0.001	0.002
B	A374P/T375N	0.002	0.004
B	I376M	0.002	ND
B	V370I/T375N	0.003	0.009
B	V218A/H219Q/V370A/ΔT371/T375A	0.077	0.145
B	V362I/N372T/A374T/T375N	0.050	0.123
B	V218A/H219Q/A326S/V370A/delT371/ S373T/T375A	0.001	0.010
C	V218A/H219Q/A326S/ΔT371/A374T/T375N	0.001	0.001
C	V218I/R286K/V370A/ΔT371/A374T/T375S	0.003	0.007
C	ΔV370/A374S/ΔT375	0.004	0.004

		EC_{50}, µM	
Subtype	Key Gag polymorphisms	GSK'254	GSK'795
C	R286K/V370A/ΔIT371/ΔA374/T375N	0.009	1.575
C	H219Q/R286K/ΔV370A/ΔT375	0.001	0.013
C	Not sequenced	0.003	0.004
A	V218A/H219Q/T332S/P339T/A340G/G357 S/V362I/V370A/T371Q/S373T/A374N	0.003	0.006
A	Not sequenced	0.001	0.002
A	Not sequenced	0.005	0.002
AE	T332S/Q369F/V370A/ΔT371/N372Q/S373 Q/T375N	0.005	0.018
AE	T332S/V370A/ΔT371/N372Q/S373N/A374 V/T375N	0.001	0.533
AE	T332S/V370A/ΔT371/N372Q/S373H/T37N	0.003	0.035

- In a second set of experiments, using a panel of 24 subtype B and 11 subtype C chimeric viruses with broad Gag diversity, GSK'254 exhibited median EC_{50} values of 1.4 nM for subtype B and C viruses

EC_{50}, concentration producing a 50% inhibitory effect.

Estimation of Target Trough Concentration for GSK'254 Based on Potency Against a Panel of Viruses With Diverse Gag Sequences



- Based on susceptibility tests of a library of 35 Gag/PR chimeric viruses from subtype B and C viruses, GSK'254 exhibited greater potency than GSK'795
- Subtype B and C viruses are expected to be sensitive to GSK'254 at an average plasma concentration at steady state of 150 nM

EC_{90}, concentration producing a 90% inhibitory effect; PBA, protein binding adjusted.

Inhibition of Cleavage of p25 by GSK'254

- In vitro mechanism-of-action studies demonstrated that GSK'254 inhibited cleavage of p25 for consensus subtype B Gag as well as Gag proteins with relevant site-directed mutants

Virus	K_{clv} min^{-1}	Half-life, min	Relative cleavage rates (vs wild-type)
Wild-type	0.0015	472	1.0
ΔV370/T371A	0.0032	219	2.2
ΔV370	0.0039	178	2.7
V362I	0.0043	161	2.9
V370A	0.0045	155	3.0
A364V	0.014	48	9.7

- GSK'254 inhibited cleavage of p25 in the A364V variant but at a 10-fold lower rate

K_{clv}, p25 cleavage constant.

Summary

- GSK’254 shows similar potency against a wide range of HIV Gag polymorphisms across various subtypes compared with wild-type
  - Cleavage rates of p25 were similar across most key Gag polymorphisms
- GSK’254 consistently demonstrated greater potency across multiple isolates than a previously developed maturation inhibitor, GSK’795
  - Subtype B and C viruses are expected to be sensitive to GSK’254 at an average plasma concentration at steady state of 150 nM
- These data demonstrate the optimized antiviral properties of GSK’254, a once-daily maturation inhibitor, against viruses with common MI-related Gag polymorphisms and support the ongoing clinical development of GSK’254 for the treatment of HIV
  - The results from a phase 2a proof-of-concept study showing efficacy with GSK’254 in people living with HIV are being presented at this conference (Presentation 1975; Tuesday, March 9, at 11:40 AM)
  - GSK’254 is currently being investigated in an ongoing phase 2b trial

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