The Initial Phase I Evaluation of the Safety, Tolerability, and Pharmacokinetics of GSK3640254, a Next-Generation HIV Maturation Inhibitor, as Assessed in Healthy Subjects

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Conflict of Interest Statement

- Samit R. Joshi is an employee of ViiV Healthcare

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Learning Objectives

- To understand the safety and tolerability of the next-generation maturation inhibitor, GSK3640254, following single and repeated daily administration at various doses
- To describe the PK of GSK3640254 following single and repeated daily administration
- To examine dose proportionality following single and repeated doses of GSK3640254
- To compare the exposure of a mesylate salt capsule with that of the bis-hydrochloride salt capsule

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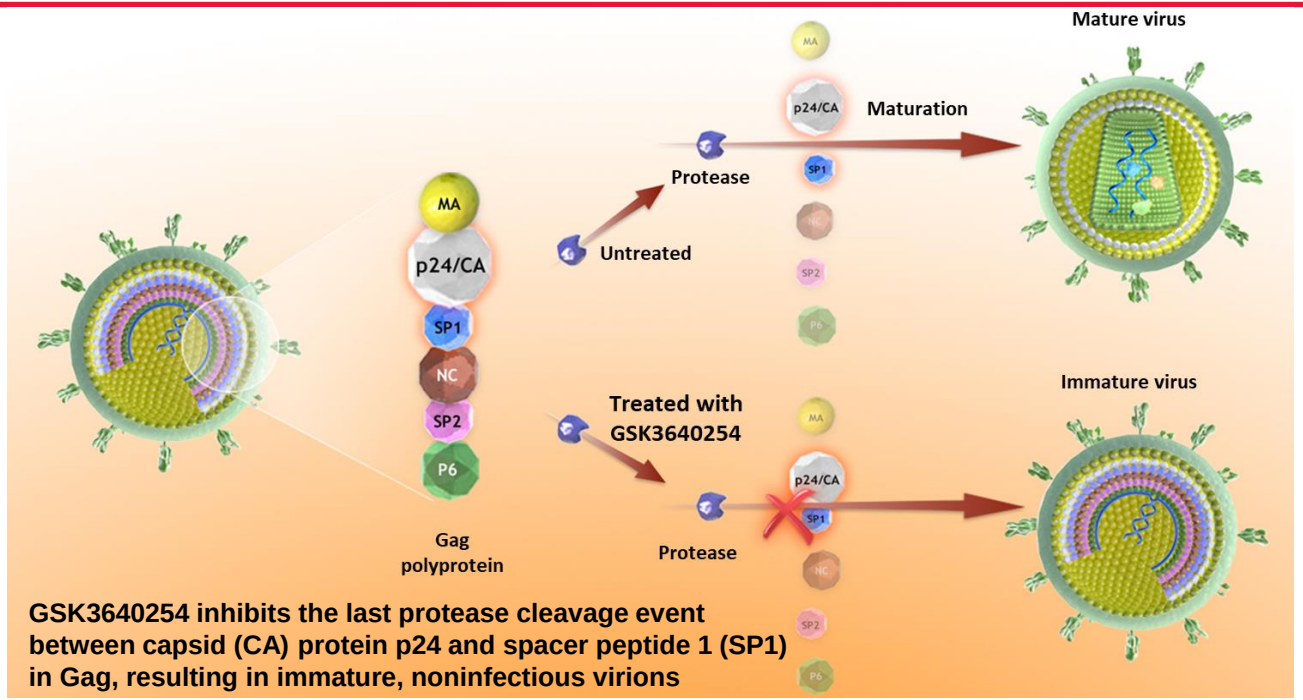
Background

- New classes of antiretrovirals are needed to address gaps in drug resistance, provide additional options to individuals with failing regimens, and avoid long-term toxicity with existing agents
- Maturation inhibitors disrupt the final step in the processing of the HIV-1 Gag protein, leading to the formation of noninfectious, immature virions[1]
- GSK3640254 is a next-generation HIV-1 maturation inhibitor with a preclinical profile that supports additional clinical evaluation for potential treatment of HIV-1 infection[2]
- We describe the safety and PK results from 2 initial phase I studies investigating GSK3640254 in healthy participants

1. Adamson et al. *Expert Opin Ther Targets.* 2009;13:895-908. **2.** ClinicalTrials.gov. clinicaltrials.gov/ct2/show/NCT03231943. Accessed April 23, 2019.

GSK3640254 Proposed Mode of Action[1-3]



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

1. Adamson et al. *Expert Opin Ther Targets.* 2009;13:895-908. **2.** Sundquist et al. *Cold Spring Harb Perspect Med.* 2012;2:7.
3. Hwang et al. CROI 2015; Seattle, WA. Abstract 114LB.

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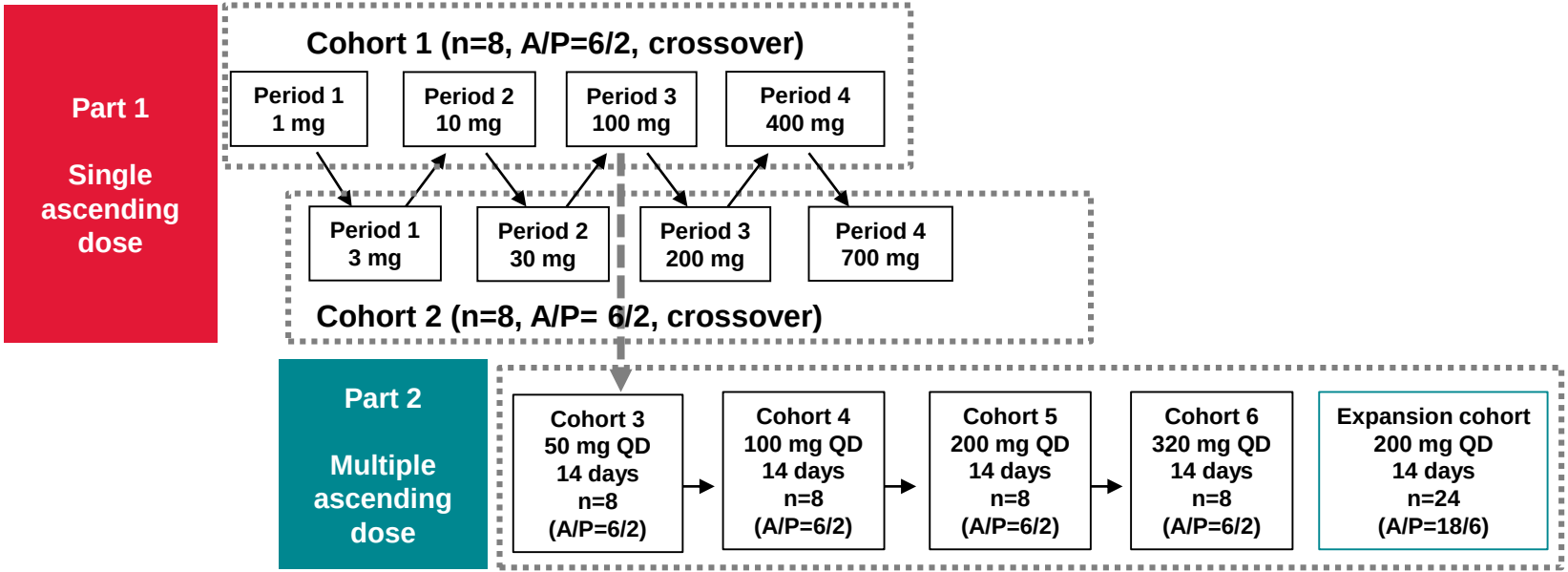
Study Design of Dose Escalation Study

Phase I, double-blind, randomized, single-center, placebo-controlled, single- and multiple-dose escalation study of GSK3640254 in healthy adults (NCT03231943)



- All doses administered after a moderate-fat meal

A, active; P, placebo; QD, once daily.

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Demographics

	SAD		MAD				
	Cohort 1 1, 10, 100, 400 mg	Cohort 2 3, 30, 200, 700 mg	Cohort 3 50 mg	Cohort 4 100 mg	Cohort 5 200 mg	Cohort 6 320 mg	Cohort 7 (expansion) 200 mg
Number of subjects planned, N	8	8	8	8	8	8	24
Number of subjects randomized, N	12	8	8	8	8	9	25
Number of subjects withdrawn (any reason), n (%)	4 (33.3)	0	0	0	0	1 (11.1)	1 (4.0)
Demographics							
Age, mean, y	39	38	35	42	38	33	36
Male sex, n (%)	12 (100)	8 (100)	8 (100)	8 (100)	8 (100)	9 (100)	25 (100)
BMI, mean, kg/m^2	26.5	26.1	27.4	25.8	25.2	25.4	24.4
White/Caucasian/European heritage, %	63	75	75	88	88	67	83

BMI, body mass index.

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Safety

Event, n	SAD		MAD			
	Cohort 1 1, 10, 100, 400 mg n=12	Cohort 2 3, 30, 200, 700 mg n=8	Cohort 3 50 mg n=8	Cohort 4 100 mg n=8	Cohort 5 + Cohort 7 (expansion) 200 mg n=33	Cohort 6 320 mg n=9
AE leading to discontinuation	3	0	0	0	1	0
AE related to study medication	1	1	3	0	3	1
All-cause AEs on GSK3640254[a]						
Grade 1 AEs	12	10	3	5	18	5
Grade 2 AEs	2	0	1	0	1	1
Grade 3/4 AEs	0	0	0	0	0	0

- No deaths or serious AEs were reported[b]

[a]In the SAD, 6 patients received GSK3640254 at each dose level. In the MAD, 6 patients in Cohorts 3 and 4, 7 patients in Cohort 6, and 25 patients in Cohort 5 + Cohort 7 received GSK3640254. [b]Drug-related AEs (grade 1 unless otherwise noted) in the SAD included abdominal pain, diarrhea, and dizziness (n=1 each), and in the MAD included nausea (n=2) and elevated transaminase, fatigue, headache (grade 2), lethargy, and maculopapular rash (n=1 each).

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Adverse Events Associated With Single Dose (n>1 Across All Doses)

AE, n (%)	1 mg (n=6)	3 mg (n=6)	10 mg (n=6)	30 mg (n=6)	100 mg (n=6)	200 mg (n=6)	400 mg (n=6)	700 mg (n=6)	Placebo (n=16)
Any event	**3 (50)**	**2 (33)**	**4 (67)**	**3 (50)**	**3 (50)**	**4 (67)**	**4 (67)**	**1 (17)**	**7 (44)**
Headache	1 (17)	0	1 (17)	1 (17)	2 (33)	1 (17)	2 (33)	0	1 (6)
Dermatitis, contact	1 (17)	1 (17)	1 (17)	0	0	1 (17)	1 (17)	0	0
Diarrhea	0	0	1 (17)	1 (17)	2 (33)	0	0	0	1 (6)
Dizziness	1 (17)	1 (17)	1 (17)	0	0	0	0	1 (17)	0
Nasal obstruction	0	0	1 (17)	0	0	0	0	0	2 (13)
Nasopharyngitis	0	0	1 (17)	0	1 (17)	0	1 (17)	0	0
Cough	0	0	1 (17)	0	1 (17)	0	0	0	0
Nightmare	0	1 (17)	0	0	0	0	0	0	1 (6)
Increased transaminases	0	0	0	0	0	1 (17)	0	0	1 (6)
Viral infection	0	0	1 (17)	0	1 (17)	0	0	0	0
Vomiting	0	0	0	0	2 (33)	0	0	0	0

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Adverse Events Associated With Multiple Doses (n>1 Across All Doses)

AE, n (%)	50 mg (n=6)	100 mg (n=6)	200 mg + expansion (n=25)	320 mg (n=7)	Placebo (n=14)
Any event	**4 (67)**	**5 (83)**	**19 (76)**	**6 (86)**	**10 (71)**
Headache	3 (50)	1 (17)	3 (12)	2 (29)	6 (43)
Dermatitis, contact	1 (17)	0	7 (28)	0	0
Dizziness	1 (17)	2 (33)	2 (8)	1 (14)	1 (7)
Contusion	1 (17)	1 (17)	3 (12)	0	1 (7)
Fatigue	2 (33)	1 (17)	1 (4)	0	2 (14)
Back pain	0	1 (17)	2 (8)	0	2 (14)
Catheter-site bruise	0	1 (17)	1 (4)	0	1 (7)
Lethargy	0	0	1 (4)	1 (14)	1 (7)
Abdominal distension	0	0	1 (4)	0	1 (7)
Abdominal pain	1 (17)	0	1 (4)	0	0
Abnormal dreams	0	0	2 (8)	0	0

AE, n (%)	50 mg (n=6)	100 mg (n=6)	200 mg + expansion (n=6)	320 mg (n=7)	Placebo (n=14)
Agitation	0	1 (17)	1 (4)	0	0
Arthropod bite	0	0	0	2 (29)	0
Catheter-site pain	0	0	0	1 (14)	1 (7)
Constipation	0	0	2 (8)	0	0
Disturbance in attention	0	0	1 (4)	0	1 (7)
Dry skin	0	0	0	1 (14)	1 (7)
Musculoskeletal stiffness	1 (17)	0	1 (4)	0	0
Nausea	0	0	1 (4)	1 (14)	0
Oropharyngeal pain	0	0	1 (4)	1 (14)	0
Rash	0	0	1 (4)	0	1 (7)
Somnolence	1 (17)	0	0	1 (14)	0
Vessel puncture site	0	0	1 (4)	0	1 (7)

Across the study cohorts, there were no clinically significant abnormal fluctuations or trends in vital signs or laboratory values. There were no abnormal clinically significant arrhythmias or QTc prolongations (values >500 milliseconds or increases >60 milliseconds from baseline).

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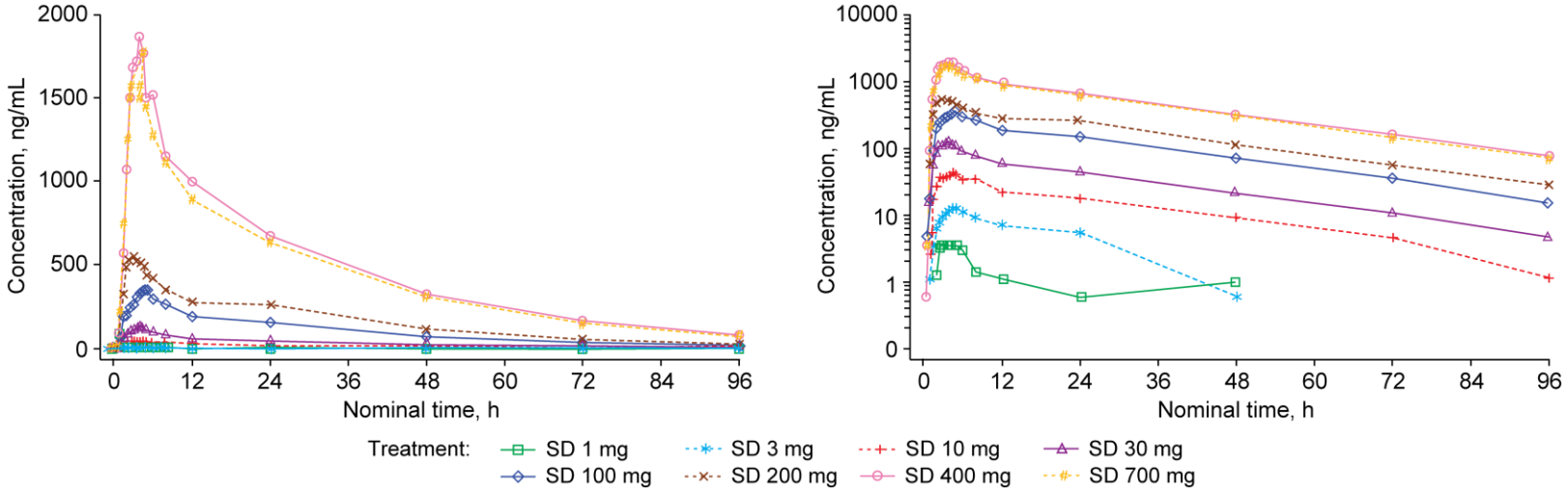
Mean Plasma GSK3640254 Concentration After Single Dose in Part 1



Geometric mean PK parameter (%CVb)[a]	1 mg (n=6)	3 mg (n=6)	10 mg (n=6)	30 mg (n=6)	100 mg (n=6)	200 mg (n=6)	400 mg (n=6)	700 mg (n=6)
$AUC_{0-\infty}$, h*µg/mL	0.057 (39)[b,c]	0.329 (34)[c]	1.227 (19)	2.992 (26)	8.539 (67)	14.952 (41)	42.989 (51)	39.692 (50)
Cmax, µg/mL	0.005 (16)	0.014 (31)	0.047 (30)	0.130 (21)	0.372 (72)	0.579 (27)	1.881 (50)	1.724 (41)
Tmax, median (range), h	3.500 (3-6)	4.500 (2-5)	3.500 (3-5)	4.000 (3-5)	3.750 (2-5)	3.000 (2-4)	3.250 (2-6)	3.250 (2-5)
$T_{1/2(z)}$, h	7.886 (35)[b]	20.486 (21)	25.332 (19)	21.221 (18)	22.838 (11)	22.620 (22)	23.737 (18)	20.761 (24)

[a]Unless otherwise noted. [b]n=3. [c]Most concentrations were below the limit of quantitation and/or the %AUC extrapolated was >20% for all subjects so this value should be interpreted with caution.

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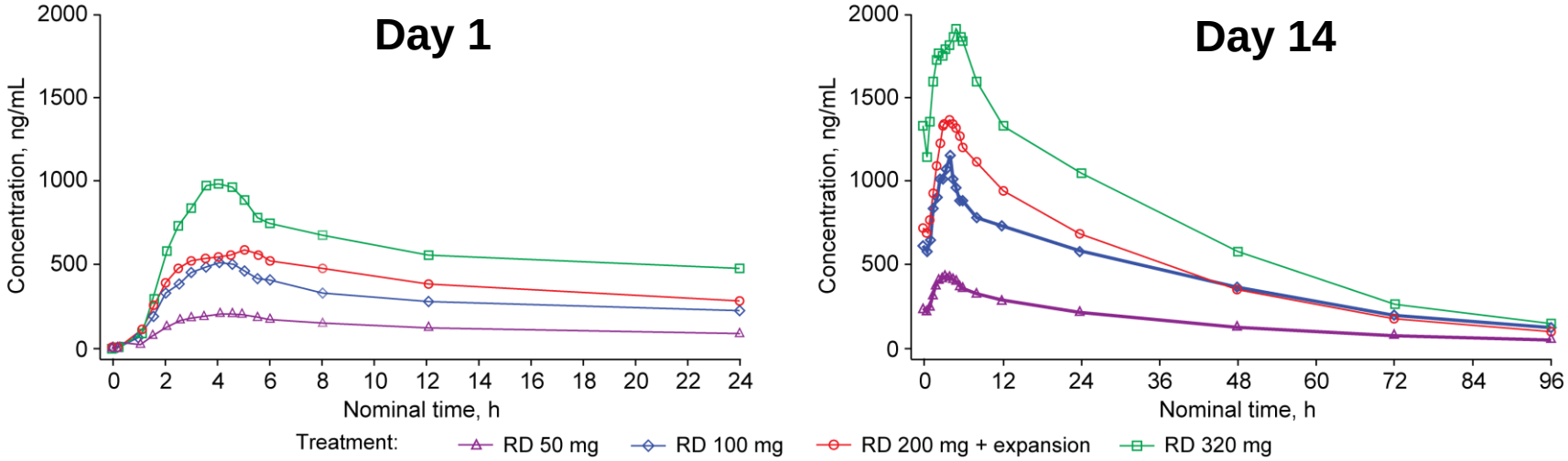
Mean Plasma GSK3640254 Concentration After Multiple Doses in Part 2



Day 14 geometric mean PK parameter (%CV)[a]	50 mg (n=6)	100 mg (n=6)	200 mg + expansion (n=24)	320 mg (n=7)
AUC_{0-24}, h*µg/mL	6.282 (34)	17.506 (14)	21.501 (34)	31.954 (35)
Cmax, µg/mL	0.414 (32)	1.182 (10)	1.402 (31)	2.156 (20)
Tmax, median (range), h	3.775 (3-5)	4.000 (2-5)	3.750 (2-6)	4.250 (2-6)
$T_{1/2(z)}$, h	24.847 (5)	28.358 (19)	22.125 (15)	22.350 (12.6)

[a]Unless otherwise noted.

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Relative Bioavailability of Mesylate Salt Capsule vs Hydrochloride Salt Capsule

- This was a single-center, 2-period, randomized, open-label, phase I, relative bioavailability study (NCT03575962)
- Healthy adults were randomized (1:1) to receive a single dose of each treatment with at least 7 days between doses
- The study used a mixed model analysis of variance on natural log-transformed PK parameters Cmax, C_{24}, $AUC_{0-\infty}$, and AUC_{0-last} for GSK3640254
- 14 participants (all male, mostly white) were included
  - Mean age was 33.9 years
  - Mean BMI was 25.4 kg/m^2

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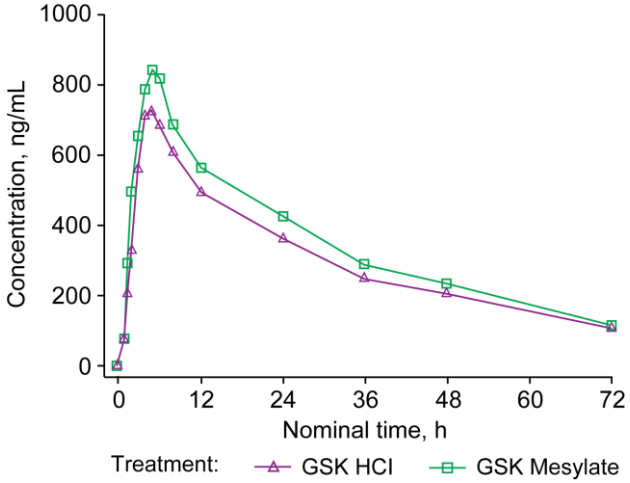
Comparison of PK Parameters Following 200-mg Single Dose of Each Formulation



PK parameter[a]	Geometric LS Mean: Bis-hydrochloride salt formulation 200 mg[b] (n=14)	Geometric LS Mean: Mesylate salt 200 mg[b] (n=14)	Ratio[c] (90% CI)
$AUC_{0\text{-last}}$, µg*h/mL	20.3	22.6	1.117 (0.99, 1.27)
Cmax, µg/mL	0.736	0.850	1.156 (0.99, 1.35)

- 2 drug-related AEs were reported (both were grade 1 headaches)
- There were no clinically significant changes in vital signs, ECG parameters, or laboratory parameters

[a]Unless otherwise noted. [b]Administered as two 100-mg capsules. [c]Ratio represents PK parameters of the mesylate salt formulation to those of the bis-hydrochloride salt formulation.

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Conclusions

- GSK3640254 did not show any clinically significant adverse tolerability findings or trends through a maximum of 14 days of dosing
- The PK profile from these studies supports once-daily dosing in HIV-1–infected patients with a range of doses that are anticipated to have antiviral activity
- The relative bioavailability of the mesylate salt formulation was comparable to that of the bis-hydrochloride salt formulation
- These data supported the evaluation of GSK3640254 in an ongoing proof-of-concept study (NCT03784079) in HIV-1–infected treatment-naive adults

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Acknowledgments

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