Clinical Infectious Diseases

MAJOR ARTICLE

Antiviral Activity, Safety, and Exposure–Response Relationships of GSK3532795, a Second-Generation Human Immunodeficiency Virus Type 1 Maturation Inhibitor, Administered as Monotherapy or in Combination With Atazanavir With or Without Ritonavir in a Phase 2a Randomized, Dose-Ranging, Controlled Trial (AI468002)

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Background. GSK3532795 is a second-generation human immunodeficiency virus type 1 (HIV-1) maturation inhibitor that targets HIV-1 Gag, inhibiting the final protease cleavage between capsid protein p24 and spacer protein-1, producing immature, noninfectious virions.

Methods. This was a phase 2a, randomized, dose-ranging multipart trial. In part A, subtype B-infected subjects received 5–120 mg GSK3532795 (or placebo) once daily for 10 days. In part B, subtype B-infected subjects received 40 mg or 80 mg GSK3532795 once daily with atazanavir (ATV) with or without (±) ritonavir (RTV) or standard of care (SOC) (tenofovir disoproxil fumarate 300 mg, emtricitabine 200 mg, and ATV/RTV 300 mg/100 mg) for 28 days. In part C, subtype C-infected subjects received 40 mg or 120 mg GSK3532795 once daily (or placebo) for 10 days. Endpoints included change in HIV-1 RNA from baseline on day 11 (parts A/C) or day 29 (part B).

Results. A >1 $\log_{10}$ median decline in HIV-1 RNA was achieved by day 11 in parts A and C and day 29 in part B at GSK3532795 doses ≥40 mg; part B subjects receiving GSK3532795 and ATV ± RTV achieved similar declines to those receiving SOC. Median of the maximum declines in HIV-1 RNA were similar for the 40–120 mg once-daily dose groups regardless of baseline Gag polymorphisms. There were no deaths, adverse events leading to discontinuation, or serious adverse events.

Conclusions. GSK3532795 demonstrated potent antiviral activity against subtype B (monotherapy or with ATV ± RTV) and subtype C, and was generally well tolerated, which supported continued development of GSK3532795 in subjects with HIV-1 subtype B or subtype C.

Clinical Trials Registration. NCT01803074.

Keywords. HIV-1 infection; GSK3532795; maturation inhibitor; phase 2a study; dose-ranging.

There is a need for antiretroviral agents with novel mechanisms of action, unique resistance profiles, good long-term tolerability and safety, and manageable drug–drug interactions. Maturation is the final stage in the proteolytic cascade leading to production of infectious virions. Blocking the HIV-1 Gag cleavage site at the p24 CA protein and spacer peptide 1 (SP1) boundary produces noninfectious virus [1, 2], and pharmacological intervention of this site is a viable therapeutic strategy (Figure 1, adapted from [3]).

A first-generation maturation inhibitor (MI), bevirimat (BVM), provided proof of concept for this class by demonstrating dose-dependent antiviral activity in phase 1 and 2 studies [4].

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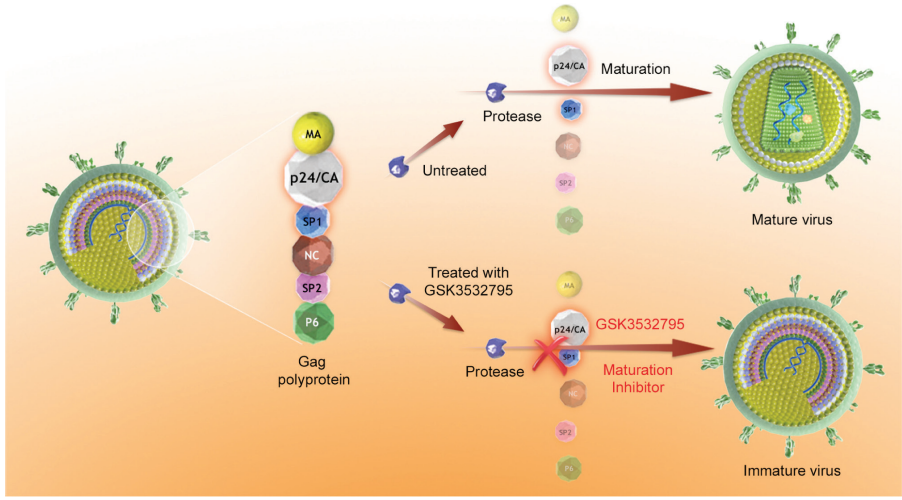

Figure 1. Mode of action of maturation inhibitors and GSK3532795 (adapted from [26]: Presented by Max Lataillade at CROI 2015; Conceptualization and Design of Mechanism of Action for HIV-1 Maturation Inhibition GSK3532795, Max Lataillade, Carey Hwang, Mark Krystal, and Ira Dicker; graphic design by Nucleus Global; funded by Bristol-Myers Squibb).

However, further development was suspended because naturally occurring Gag polymorphisms conferring BVM resistance were found in approximately 50% of HIV-1–infected subjects [5].

GSK3532795 (formerly BMS-955176) is a second-generation HIV-1 MI that inhibits a specific HIV-1 protease-mediated cleavage event between CA and SP1 in the Gag polyprotein, resulting in the production of immature, noninfectious virus particles (Figure 1) [3]. GSK3532795 mode of action is different to that of protease inhibitors (PIs), which target the protease enzyme rather than the Gag substrate. In vitro studies show that GSK3532795 binds reversibly to HIV-1 Gag with greater affinity than BVM [6, 7] and is active against HIV-1 subtypes B, C, and AE [6–8], including those with naturally occurring Gag polymorphisms that are associated with reduced BVM activity [5, 7, 9]. GSK3532795 also shows in vitro activity against clinical isolates resistant to PIs, nucleos(t)ide reverse transcriptase inhibitors (NRTIs), nonnucleos(t)ide reverse transcriptase inhibitors (NNRTIs), and integrase strand transfer inhibitors (INSTIs) [6]. In healthy subjects, GSK3532795 is rapidly absorbed with a half-life ($T_{1/2}$) of approximately 35 hours and is eliminated principally via cytochrome P450 (CYP) 3A4 metabolism followed by excretion in bile, with little renal excretion (Bristol-Myers Squibb, data on file).

AI468002 was a phase 2a dose-ranging study that evaluated the antiviral activity of GSK3532795 monotherapy in subjects infected with HIV-1 subtype B or subtype C. In subtype B-infected subjects, GSK3532795 was also studied with (+) atazanavir (ATV), with or without (±) ritonavir (RTV), and compared against a standard-of-care (SOC) combination antiretroviral therapy (cART) regimen. GSK3532795 safety, pharmacokinetics, and exposure–response were secondary outcomes.

MATERIALS AND METHODS

Study Design

AI468002 was a 3-part, sequential, randomized, double-blind or open-label, multiple-dose study conducted at sites in Germany, the United Kingdom, and South Africa between 4 April 2013 and 29 November 2014. Subjects were screened for eligibility within 30 days prior to dosing on day 1, admitted to the clinical facility on day −1, and confined for the dosing period, except those recruited to part B. Subjects were asked to commit to follow-up outpatient visits for clinical safety, pharmacokinetics, and pharmacodynamics sample collection.

In part A, 40 subjects with HIV-1 subtype B were randomized 1:1:1:1 to GSK3532795 once-daily (QD) dose groups of 5, 10, 20, or 40 mg, then randomized 4:1 within each dose group to receive either GSK3532795 or placebo QD for 10 days (Figure 2A). In part B, 20 subjects with HIV-1 subtype B were randomized 2:2:1 to QD dose groups of GSK3532795 40 mg + ATV 400 mg; GSK3532795 40 mg + ATV/RTV 300 mg/100 mg; and a SOC of tenofovir disoproxil fumarate (TDF) 300 mg + emtricitabine (FTC) 200 mg (fixed-dose combination) + ATV/RTV 300 mg/100 mg, each administered for 28 days (Figure 2B). In part C, 10 HIV-1 subtype C-infected subjects were randomized 4:1 to receive either 40 mg GSK3532795 QD or placebo QD for 10 days, respectively (Figure 2C). The GSK3532795 80 mg and 120 mg dose groups (in part B as GSK3532795 80 mg + ATV 400 mg) were included as an amendment to the original protocol after analysis of data for doses ≤40 mg from part A.

Randomization occurred before dosing on day 1 using a computer-generated scheme. In parts A and C, GSK3532795 or placebo was administered double-blind as an oral suspension

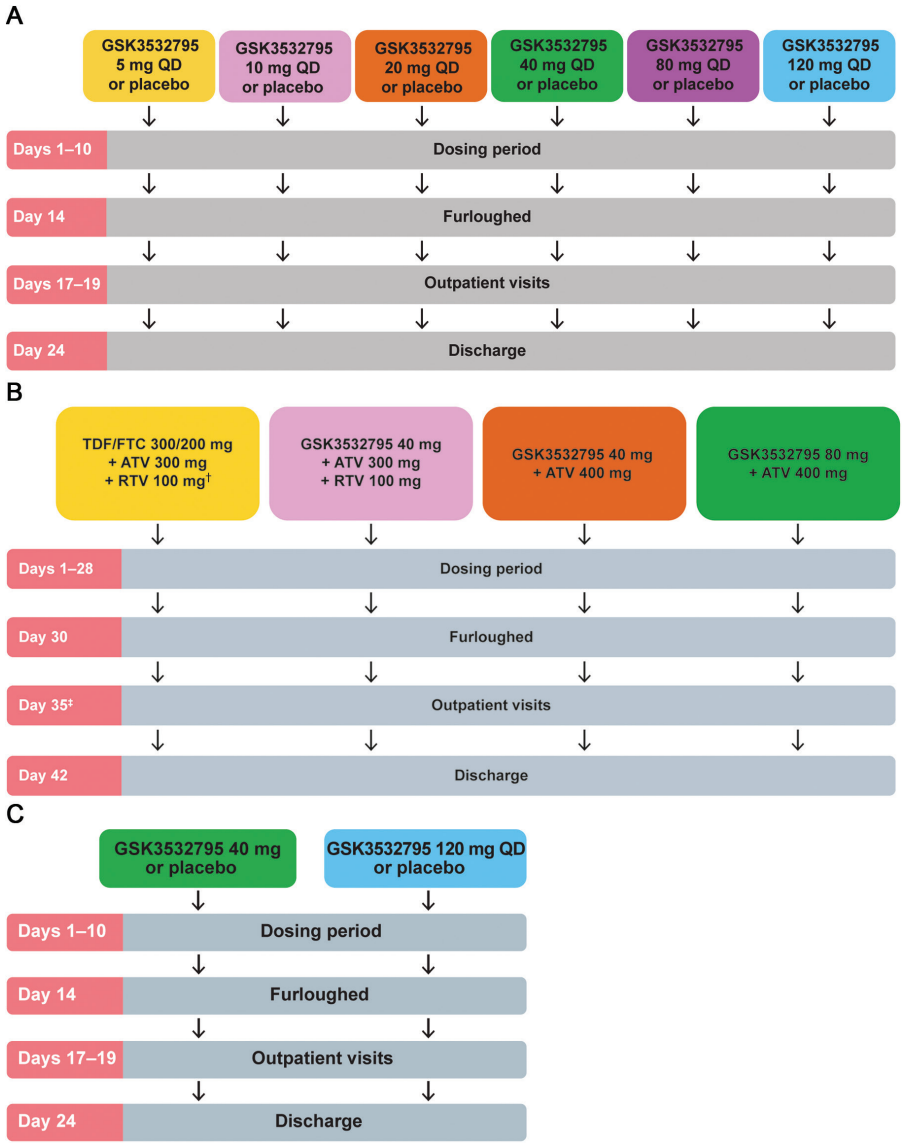

Figure 2. AI468002 study design. *A*, Part A. *B*, Part B. *C*, Part C. †Standard-of-care control group. Tenofovir disoproxil fumarate/emtricitabine given as a fixed-dose combination. All doses were once daily. ‡Or per investigator's discretion. Abbreviations: ATV, atazanavir; FTC, emtricitabine; QD, once daily; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

after at least a 10-hour fast on days 1–10. In part B, GSK3532795 and ATV ± RTV, or SOC, was administered open-label as an oral suspension with breakfast from days 1 to 28.

Ethical Considerations

All subjects provided written informed consent, and the study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the institutional review board at the study sites.

Subjects

Eligible subjects were 18–55 years, infected with HIV-1 subtype B or C, who had plasma HIV-1 RNA level ≥5000 copies/mL and a $CD4^+$ T-cell count ≥200 cells/μL. Only male HIV-1 subtype B-infected subjects were recruited to part B. Subjects could be antiretroviral treatment-naive (defined as <1 week of antiretroviral therapy) or treatment-experienced (but PI and MI naive).

Subjects with a history of genotypic/phenotypic drug resistance to PIs or with HIV-1 genotypic drug resistance at baseline (primary PI resistance mutations including D30N, M46I/L, I47V/A, G48V, I50L, I54M/L, Q58E, T74P, L76V, V82A/F/L/T/S, N83D, I84V, N88S, or L90M) were excluded.

Subjects with protocol-defined abnormal findings of physical, electrocardiographic (ECG), and/or laboratory examinations were excluded, as were subjects with hepatitis B or C virus coinfection. In parts A and C, women of childbearing potential were required to use at least 2 predefined

methods of contraception throughout the study and for a total of 38 days after the last dose of study medication. A negative result of a serum or urine pregnancy test within 24 hours prior to receiving study medication on day 1 was required.

Study Outcomes

The primary objective was to assess antiviral activity (median change from baseline in $\log_{10}$ HIV-1 RNA) following administration of GSK3532795 for 10 days (parts A and C) or 28 days (part B).

Secondary objectives were to assess the safety, tolerability, and pharmacokinetics of GSK3532795 administered as monotherapy or with ATV ± RTV, the effect of administering ATV ± RTV on the antiviral activity of GSK3532795, and the relationship between antiviral activity and plasma exposure of GSK3532795 given as monotherapy. Median of the maximum change in HIV-1 RNA from baseline to study discharge was measured for all 3 parts.

Assessments

Plasma HIV-1 RNA was measured in parts A and C at screening and on days 1–14, 17, 19, and 24–26; and in part B at screening and on days 1–28, 29, 30, 35, and 42. Plasma HIV-1 RNA was quantified using the Abbott m2000 RealTime System (Abbott Molecular, Des Plaines, Illinois).

Safety assessments, including vital signs and physical examination, adverse events (AEs), laboratory measurements, and ECG were recorded throughout the study. AEs were coded according to MedDRA version 17.1. Investigators assessed the severity of AEs and their relationship to study drugs.

Pharmacokinetics, Exposure–Response, and Statistical Analysis

Serial pharmacokinetic blood samples for noncompartmental and exposure–response analyses were collected on days 1 and 10, and trough samples on days 2, 4, 6, and 8. Plasma concentrations of GSK3532795 were determined via a validated liquid chromatography/mass spectrometry method. Dose proportionality was assessed using the power model fitted to the log-transformed exposure and log-scale dose. The exposure–response relationship was assessed using a nonlinear, 3-parameter sigmoid E_{max} equation,

$Y = E_0 + E_{max} * C / (EC_{50}$ [half maximal effective concentration] $+C)$.

where C, observed plasma concentration at 24 hours value on day 10; E_{max}, maximum possible effect (at infinite C) below E_0 (response predicted when C is 0); EC_{50}, C producing 50% of E_{max}; Y, effect at concentration C.

AI468002 was designed such that 8 subjects per dose group were treated with an active dose of GSK3532795; with this sample size, there was an ≥83% probability to observe an estimated median decrease in plasma HIV-1 RNA levels from baseline of ≥1 $\log_{10}$ IU/mL, if the underlying response rate of achieving ≥1 $\log_{10}$ IU/mL was 60% or higher. At this sample size, there was also an 80% probability of observing ≥1 AE with an underlying event rate of ≥19%.

RESULTS

Subject Disposition and Baseline Characteristics

One hundred seven subjects were randomized and treated; all completed the study (Figure 3). Sixty, 28, and 19 eligible subjects were assigned to parts A, B, and C, respectively. Ninety-nine

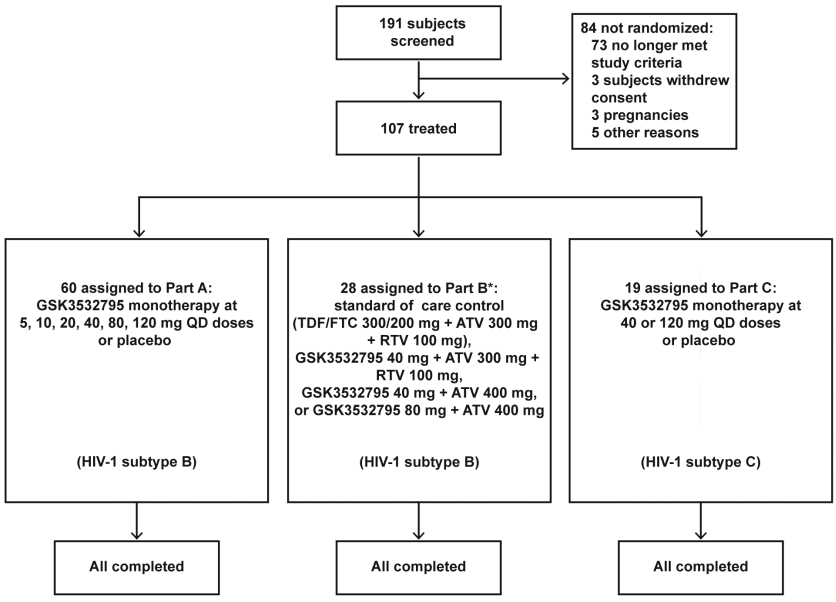

Figure 3. Subject randomization and flow. *All doses were once daily. Abbreviations: ATV, atazanavir; FTC, emtricitabine; HIV-1, human immunodeficiency virus type 1; QD, once daily; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

Table 1. AI468002 Baseline Characteristics by Study Part

GSK3532795 Monotherapy in Fasted HIV-1 Subtype B-Infected Subjects (Part A)[a]							
		GSK3532795					
Characteristic	Placebo (n = 12)	5 mg (n = 8)	10 mg (n = 8)	20 mg (n = 8)	40 mg (n = 8)	80 mg (n = 8)	120 mg (n = 8)
Median age, y	36.0	43.5	39.0	33.0	38.0	31.5	37.5
Male sex, No. (%)	12 (100)	8 (100)	7 (87.5)	8 (100)	8 (100)	8 (100)	8 (100)
Race, No. (%)							
White	12 (100)	6 (75.0)	7 (87.5)	8 (100)	8 (100)	8 (100)	8 (100)
Black	0	0	1 (12.5)	0	0	0	0
Other	0	2 (25.0)	0	0	0	0	0
Mean HIV-1 RNA, $\log_{10}$ copies/mL	3.9	4.0	4.0	3.7	4.0	4.0	3.8
Mean $CD4^+$ T-cell count, cells/μL	475.5	411.0	522.0	526.0	511.5	537.3	514.5

GSK3532795 Monotherapy in Fasted HIV-1 Subtype C-Infected Subjects (Part C)[a]			
Treatment	Placebo (n = 4)	GSK3532795 40 mg (n = 8)	GSK3532795 120 mg (n = 7)
Median age, y	33.0	35.5	38.0
Male sex, No. (%)	2 (50.0)	5 (62.5)	5 (71.4)
Race, No. (%)			
White	0	2 (25.0)	0
Black	3 (75.0)	5 (62.5)	7 (100)
Other	1 (25.0)	1 (12.5)	0
Mean HIV-1 RNA, $\log_{10}$ copies/mL	3.9	4.2	4.0
Mean $CD4^+$ T-cell count, cells/μL	389.3	542.0	428.0

GSK3532795 + ATV ± RTV in Fed HIV-1 Subtype B-Infected Subjects (Part B)[a]				
Treatment	TDF/FTC 300/200 mg + ATV 300 mg + RTV 100 mg[b] (n = 4)	GSK3532795 40 mg + ATV 300 mg + RTV 100 mg (n = 8)	GSK3532795 40 mg + ATV 400 mg (n = 8)	GSK3532795 80 mg + ATV 400 mg (n = 8)
Median age, y	32.5	34.0	32.5	31.5
Male sex, No. (%)	4 (100)	8 (100)	8 (100)	8 (100)
Race, No. (%)				
White	4 (100)	8 (100)	6 (75.0)	7 (87.5)
Black	0	0	0	1 (12.5)
Other	0	0	2 (25.0)	0
Mean HIV-1 RNA, $\log_{10}$ copies/mL	4.11	4.25	4.07	4.10
Mean $CD4^+$ T-cell count, cells/μL	475.0	546.8	629.6	575.6

Summary of Baseline Characteristics for All Parts	
Median age, y	36.1
Male sex, No. (%)	99 (92.5)
Race, No. (%)	
White	84 (78.5)
Black	17 (15.9)
Other	5 (4.7)
Mean HIV-1 RNA, $\log_{10}$ copies/mL	4.44
Mean $CD4^+$ T-cell count, cells/μL	511.1

Abbreviations: ATV, atazanavir; FTC, emtricitabine; HIV-1, human immunodeficiency virus type 1; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

[a]All doses were administered once daily.

[b]Standard-of-care control group; TDF/FTC given as a fixed-dose combination.

subjects (92.5%) were male and 84 (78.5%) white. Mean age was 36.1 years, mean baseline HIV-1 RNA was 4.01 $\log_{10}$ copies/mL, and mean baseline CD4+ T-cell count was 511.1 cells/μL (Table 1).

GSK3532795 Monotherapy (5–120 mg QD) in HIV-1 Subtype B (Part A)

Median declines (baseline to day 11) in HIV-1 RNA of >1 $\log_{10}$ copies/mL were observed consistently from approximately day 7 with GSK3532795 doses of 40–120 mg QD (Figure 4A). Across all GSK3532795 groups, median of the maximum change in HIV-1 RNA from baseline to study discharge on day 24 ranged from −0.50 to −1.70 $\log_{10}$ copies/mL; the greatest change was observed with the 40 mg QD dose (Figure 4B). At doses of 40–120 mg QD, the decline in HIV-1 RNA remained >1 $\log_{10}$ copies/mL for an additional week in most subjects, likely due to the long plasma $T_{1/2}$ of GSK3532795.

Despite small sample sizes (n = 15 for subjects with baseline Gag polymorphisms and n = 8 for subjects without),

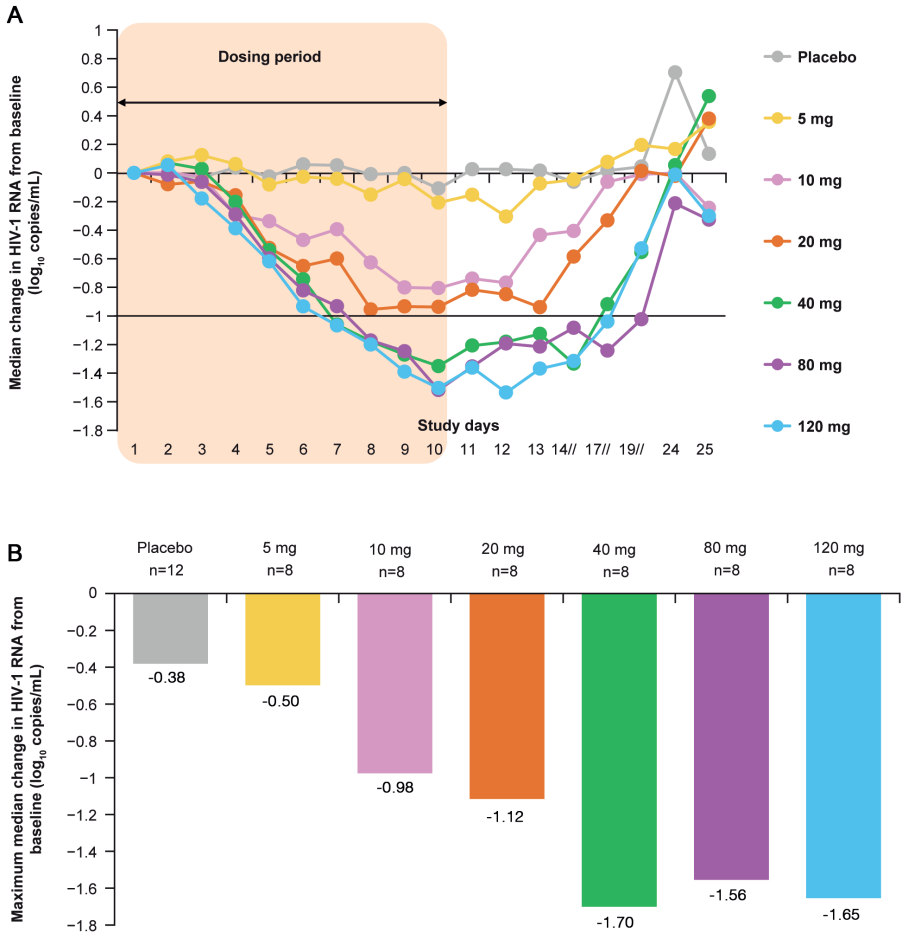

Figure 4. Median change in human immunodeficiency virus type 1 (HIV-1) RNA over time (*A*) and median of the maximum change in HIV-1 RNA between baseline and day 24 (study discharge) (*B*) in part A (GSK3532795 monotherapy given to subjects infected with HIV-1 subtype B). All doses were administered once daily.

medians of the maximum declines in HIV-1 RNA were similar for the GSK3532795 40–120 mg QD doses, regardless of the presence of baseline Gag polymorphisms evaluated at positions 362, 369, and 370 [5–7, 9–16] (Figure 5); the range of median of the maximum decline in HIV-1 RNA was −1.43 to −1.98 $\log_{10}$ copies/mL in the presence of baseline Gag polymorphisms and −1.55 to −1.75 $\log_{10}$ copies/mL in their absence. Only 1 subject in the 20 mg QD dose group with baseline Gag polymorphisms had a <1 $\log_{10}$ copies/mL decline in HIV-1 RNA.

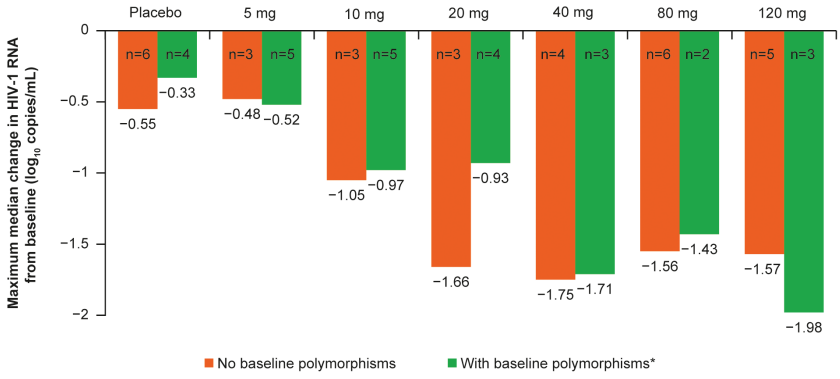

Figure 5. Median of the maximum change in human immunodeficiency virus type 1 (HIV-1) RNA by baseline Gag polymorphisms in part A (GSK3532795 monotherapy given to subjects infected with HIV-1 subtype B). *Baseline polymorphisms at Gag V362, A364, Q369, and V370 were evaluated, but no baseline polymorphisms at position 364 were present in the study. Samples with polymorphisms at position 371 were susceptible to GSK3532795 in vitro and in study AI468002.

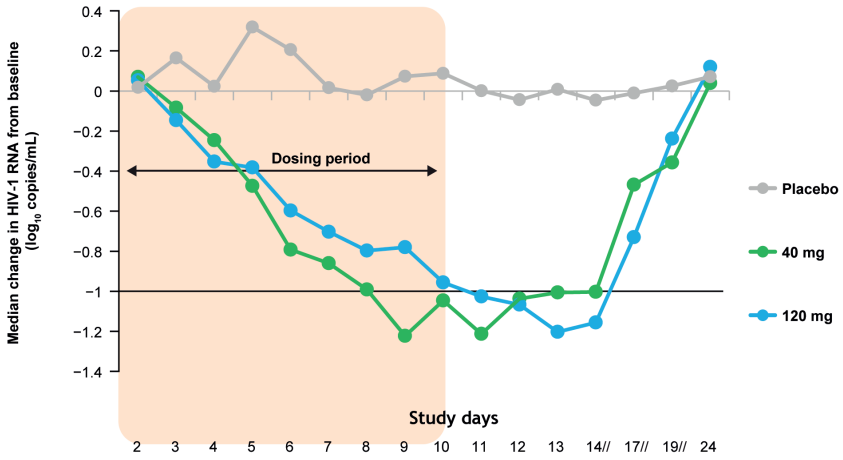

Figure 6. Median change in human immunodeficiency virus type 1 (HIV-1) RNA over time in part C (GSK3532795 monotherapy given to subjects infected with HIV-1 subtype C). All doses were administered once daily.

GSK3532795 Monotherapy (40–120 mg QD) in HIV-1 Subtype C (Part C)

Median declines (baseline to day 11) in HIV-1 RNA of >1 $\log_{10}$ copies/mL was observed after day 8 for 40 mg QD and day 10 for 120 mg QD (Figure 6). HIV-1 RNA continued to decline following cessation of treatment on day 10, and up to day 14 for both doses. For the 40-mg and 120-mg QD dose groups, median of the maximum change from baseline in HIV-1 RNA was −1.35 $\log_{10}$ copies/mL and −1.26 $\log_{10}$ copies/mL, respectively, compared with −0.42 $\log_{10}$ copies/mL for placebo (Supplementary Figure 1). Importantly, all subjects in part C had ≥1 of the 3 predefined Gag polymorphisms at baseline.

GSK3532795 + ATV ± RTV in HIV-1 Subtype B (Part B)

Median declines at day 29 ranged from −1.66 to −2.18 $\log_{10}$ copies/mL for the GSK3532795 groups + ATV ± RTV and −2.22 $\log_{10}$ copies/mL for the SOC group. For all GSK3532795 groups, the decline was observed after the last day of dosing on day 28 to approximately day 35 (Figure 7). Median of the maximum change in HIV-1 RNA from baseline to study discharge on day 42 was −1.86 and −2.23 $\log_{10}$ copies/mL for the 40 mg and 80 mg GSK3532795 + ATV groups, respectively, and −2.20 $\log_{10}$ copies/mL for 40 mg GSK3532795 + ATV/RTV, compared with −2.39 $\log_{10}$ copies/mL for SOC (Supplementary Figure 2).

Safety

In part A, all AEs were mild to moderate and the most common were transient headache (n = 24), abnormal dreams (n = 14), and night sweats (n = 5) (Supplementary Table 1). The proportion of subjects with AEs was similar in the GSK3532795 and placebo groups. In part C, all AEs were mild to moderate and the most common was headache (n = 9), and the proportion of

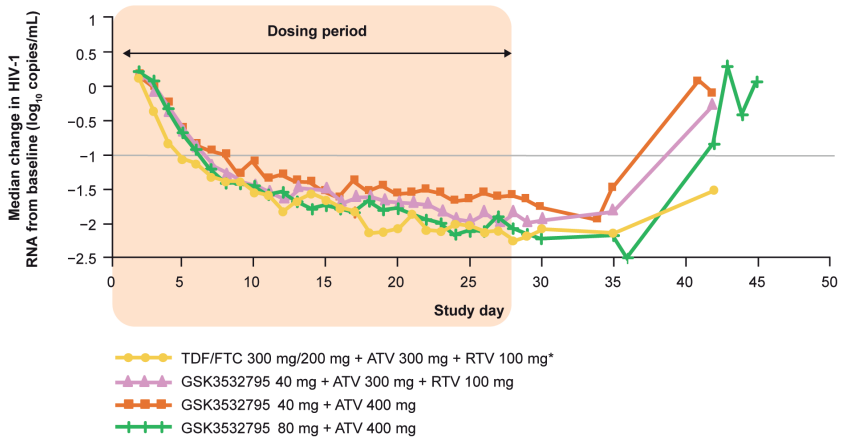

Figure 7. Median change in human immunodeficiency virus type 1 (HIV-1) RNA over time in part B (GSK3532795 combined with atazanavir [ATV] ± ritonavir [RTV] given to subjects infected with HIV-1 subtype B). All doses were administered once daily. *Standard-of-care control group. Tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) given as a fixed-dose combination. Abbreviations: ATV, atazanavir; FTC, emtricitabine; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

Table 2. AI468002 Safety Summary by Study Part

	Parts A and C[a]						
		GSK3532795					
Subjects, n (%)	Placebo (n = 16)[b]	5 mg (n = 8)	10 mg (n = 8)	20 mg (n = 8)	40 mg (n = 16)[b]	80 mg (n = 8)	120 mg (n = 15)[b]
Any AE	8 (50.0)	5 (62.5)	4 (50.0)	4 (50.0)	8 (50.0)	7 (87.5)	10 (66.6)
Discontinuations due to AE(s)	0	0	0	0	0	0	0
Serious AEs	0	0	0	0	0	0	0
Grade 3–4 related AEs	0	0	0	0	0	0	0
Laboratory abnormalities (grade 3–4)	0	0	0	0	0	0	1 (6.7)[c]
Deaths	0	0	0	0	0	0	0

	Part B[a]			
Subjects, n (%)	TDF/FTC 300/200 mg + ATV 300 mg + RTV 100 mg (n = 4)[d]	GSK3532795 40 mg + ATV 300 mg + RTV 100 mg (n = 8)	GSK3532795 40 mg + ATV 400 mg (n = 8)	GSK3532795 80 mg + ATV 400 mg (n = 8)
Any AEs	4 (100.0)	8 (100.0)	8 (100.0)	6 (75.0)
Discontinuations due to AE(s)	0	0	0	0
Serious AEs	0	0	0	0
Grade 3–4 related-AEs	0	0	0	1 (12.5)[e]
Laboratory abnormalities (grade 3–4)	3 (75.0)	5 (62.5)	2 (25.0)	1 (12.5)[e]
Decreased neutrophils (absolute)	0	0	0	1 (12.5)
Bilirubin (total)[f]	3 (75.0)	5 (62.5)	2 (25.0)	0
Deaths	0	0	0	0

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AE, adverse event; ATV, atazanavir; FTC, emtricitabine; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

[a]All doses were administered once daily.

[b]Includes data from part C.

[c]Grade 3 transient neutropenia reported as related to GSK3532795.

[d]Standard-of-care control arm; TDF/FTC given as a fixed-dose combination.

[e]One subject had both an AE and a laboratory abnormality related to transient neutropenia.

[f]Due to ATV.

subjects with AEs was similar between the GSK3532795 and placebo groups. There was no apparent relationship between the GSK3532795 dose and incidence or intensity of AEs during monotherapy, aside from diarrhea, which occurred at a higher frequency at higher GSK3532795 doses.

In part B with ATV ± RTV, the most common AEs were increased bilirubin (n = 18), headache (n = 14), and diarrhea (n = 10) (Supplementary Table 1). Fewer subjects who received GSK3532795 + ATV alone (n = 2) experienced hyperbilirubinemia compared with those who received ATV/RTV (n = 5), consistent with the known safety profile of ATV [17, 18].

Twelve grade 3–4 laboratory abnormalities were reported during the study. Two cases of neutropenia were reported: 1 was reported as GSK3532795 related by the investigator in part A and the other as nonstudy related in part B (also reported as a grade 3–4 AE; this grade 3 event occurred twice during study drug administration and upon discharge remained a grade 2 abnormality). Elevated bilirubin (grade 3–4) was reported in 10 subjects in part B with ATV ± RTV. GSK3532795 + ATV alone was associated with lower median changes from baseline in bilirubin compared with groups that included ATV/RTV (Supplementary Figure 3). There were no cases of hyperbilirubinemia during GSK3532795 monotherapy. Thus, all AEs in part B were mild to moderate except for the grade 3–4 AE of neutropenia in 1 patient.

No serious AEs or deaths were reported, and no subject discontinued because of an AE (Table 2). No clinically relevant changes in vital signs, ECGs, or physical examination findings were observed.

Pharmacokinetics

Plasma pharmacokinetic parameters for GSK3532795 are listed in Table 3. In part A where subjects received GSK3532795 QD

Table 3. Plasma Pharmacokinetic Parameters for GSK3532795 Following Oral Once-Daily Administration

GSK3532795 Monotherapy in Fasted HIV-1 Subtype B-Infected Subjects (Part A)[a]						
	GSK3532795					
Parameter	5 mg (n = 8)	10 mg (n = 8)	20 mg (n = 8)	40 mg (n = 8)	80 mg (n = 8)	120 mg (n = 8)
C_{max}, ng/mL (%CV)	170.8 (20.8)	337.4 (20.9)	705.1 (15.4)	1476.2 (17.2)	2466.4 (22.1)	2809.7 (25.5)
AUC_{tau}, ng × h/mL (%CV)	2720.2 (20.7)	5168.6 (23.6)	11751.8 (15.1)	22984.8 (17.2)	39341.1 (24.2)	44182.4 (27.0)
C_{24}, ng/mL (%CV)	81.6 (23.1)	138.8 (34.1)	325.9 (19.4)	713.1 (21.9)	1150.4 (31.5)	1289.0 (26.8)
T_{max}, median h (min–max)	3 (2–4)	3 (1.5–4)	4 (3–16)	3 (2–6)	3 (1.5–4)	2.5 (1.5–3.9)
$T_{1/2}$, mean h (SD)	32.7 (6.2)	33.1 (7.9)	29.7 (6.1)	33.8 (6.3)	30.0 (4.6)	34.9 (3.0)

GSK3532795 + ATV ± RTV in Fed HIV-1 Subtype B–Infected Subjects (Part B)[a]			
Parameter	GSK3532795 40 mg + ATV 300 mg + RTV 100 mg (n = 8)	GSK3532795 40 mg + ATV 400 mg (n = 8)	GSK3532795 80 mg + ATV 400 mg (n = 8)
C_{max}, ng/mL (%CV)	1852.0 (33.6)	1667.8 (30.2)	3159.181 (22.1)
AUC_{tau}, ng × h/mL (%CV)	34225.1 (30.6)	31406.3 (31.7)	59915.7 (16.3)
C_{24}, ng/mL (%CV)	1163.2 (30.9)	1099.3 (37.0)	2010.7 (19.9)
T_{max}, median h (min–max)	5 (4–6)	4.5 (0–12)	4.5 (3–6)

GSK3532795 Monotherapy in Fasted HIV-1 Subtype C-Infected Subjects (Part C)[a]		
Parameter	GSK3532795 40 mg (n = 8)	GSK3532795 120 mg (n = 7)
C_{max}, ng/mL (%CV)	1560.122 (17.4)	3377.967 (32.8)
AUC_{tau}, ng × h/mL (%CV)	25556.638 (20.4)	53972.706 (30.2)
T_{max}, median h (min–max)	3.00 (2.00–6.00)	3.00 (1.55–4.00)

Abbreviations: %CV, coefficient of variation; ATV, atazanavir; AUC_{tau}, area under the plasma concentration-time curve in one dosing interval (time zero to 24 hours post-dose); C_{max}, maximum observed plasma concentration; C_{24}, observed plasma concentration at 24 hours; HIV-1, human immunodeficiency virus type 1; RTV, ritonavir; SD, standard deviation; T_{max}, time of maximum observed plasma concentration; $T_{1/2}$, plasma half-life.

[a]All doses were administered once daily.

as monotherapy in the fasted state, exposure increased in a less than dose-proportional manner over the entire dose range with estimated slopes of 0.914 (90% confidence interval [CI], .862–.966) and 0.914 (90% CI, .859–.969) for the maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve in one dosing interval (time zero to 24 hours post-dose) (AUC_{tau}), respectively. Up to 40 mg, exposures increase in proportion with dose; however, at doses >40 mg, increase in exposure was less than dose-proportional, with significant overlap in exposures between 80 mg and 120 mg. Median time of maximum observed plasma concentration (T_{max}) was 3 hours and similar across the dose range with GSK3532795 monotherapy. $T_{1/2}$ was approximately 30–35 hours. In part B, subjects received GSK3532795 QD + ATV ± RTV in the fed state, and exposures increased in proportion to dose (~2-fold) between 40 mg and 80 mg GSK3532795 coadministered with ATV alone. Additionally, AUC increased approximately 40% and 50%, respectively, when compared with the same doses given as monotherapy. Exposures were slightly higher (~10%) following administration of GSK3532795 40 mg with ATV/RTV relative to administration with ATV alone. T_{max} was delayed approximately 1–2 hours with ATV ± RTV in the fed state. In part C, there was a less than dose-proportional (~2-fold) increase in C_{max} and AUC_{tau} following administration of GSK3532795 40 mg and 120 mg monotherapy.

Exposure–Response Relationship

The relationship between maximum change in HIV-1 RNA from baseline vs GSK3532795 steady-state observed plasma concentration at 24 hours (C_{24}) is depicted in Figure 8. An apparent response plateau was achieved at GSK3532795 C_{24} ≥500 ng/mL. Consistent with dose response, predicted maximum decline in HIV-1 RNA from baseline is approximately 1.7 log_{10} copies/mL.

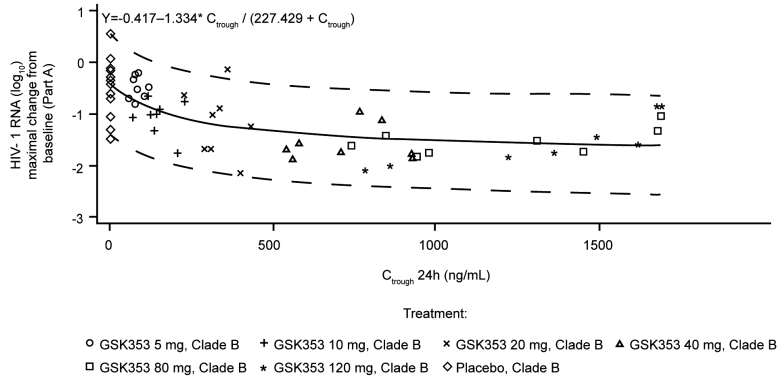

Figure 8. Maximum change from baseline in plasma $\log_{10}$ human immunodeficiency virus type 1 (HIV-1) RNA levels vs C_{trough} (24-hour) plasma concentration (part A). The exposure–response relationship was assessed using a nonlinear, 3-parameter sigmoid E_{max} equation, $Y = E0 + E_{max}*C/(EC_{50} + C)$. Placebo observations from each treatment group were combined into a single placebo group. Solid line represents the predicted relationship and dashed lines represent the 5th and 95th percentiles. Abbreviations: C, observed plasma concentration at 24 hours value on day 10; E0, response predicted when C is 0; E_{max}, maximum possible effect (at infinite C) below E0; EC_{50}, C producing 50% of E_{max}; Y, effect at concentration C.

DISCUSSION

MIs are a novel mechanistic class of antiretrovirals that may provide new alternatives for cART regimens. The first-generation MI, BVM, was associated with poor biopharmaceutical properties [19] and high protein binding (>99%) [7, 20], which necessitated a high dose to achieve target exposures following QD dosing. Importantly, BVM was not effective in HIV-1–infected subjects with naturally occurring Gag polymorphisms [5].

In this study, GSK3532795, a second-generation MI, demonstrated potent antiviral activity against HIV-1 subtype B and subtype C. A >1 $\log_{10}$ decline in HIV-1 RNA was observed in the 20–120 mg QD dose groups with a median maximum decline of 1.70 $\log_{10}$ copies/mL following 10 days of monotherapy in subtype B–infected subjects. A plateau of approximately 1.64 $\log_{10}$ copies/mL was observed at 40–120 mg QD dose groups; exposures did not increase in proportion to dose across the 40–120 mg QD dose groups. Notably, GSK3532795 doses within 40–120 mg QD produced similar median of the maximum changes in HIV-1 RNA in the presence and absence of Gag polymorphisms associated with BVM resistance [5]. A >1 $\log_{10}$ decline in HIV-1 RNA was observed following 10 days of 40 mg or 120 mg QD monotherapy in subtype C–infected subjects who had ≥1 of 3 Gag polymorphisms at baseline. As in vitro data have shown similar susceptibility profiles between subtype C and subtype AE, GSK3532795 is expected to be potent against HIV-1 subtype AE, indicating broad antiviral activity across global subtypes. Subjects were not given antiretrovirals after study discharge, so the extended viral suppression observed after the end of drug intake may be attributed to the long $T_{1/2}$ of GSK3532795.

GSK3532795 was evaluated with ATV ± RTV, because GSK3532795 and ATV inhibit late stages of the HIV viral life cycle in close proximity, but through different mechanisms; thus, potent activity when coadministered is possible. GSK3532795 80 mg + ATV 400 mg QD and GSK3532795 40 mg + ATV/RTV 300 mg/100 mg QD demonstrated similar antiviral activity (~2.2 $\log_{10}$ copies/mL median decline) compared with SOC over the 28-day treatment period; exposures to GSK3532795 + ATV alone in the fed state increased up to 50% compared with the same dose given as monotherapy fasted. This is preliminary evidence that GSK3532795 could potentially be administered as part of cART, including in PI booster– and/or nucleot(s)ide-sparing strategies that could alleviate short- and long-term toxicities associated with such agents [18, 21–24]. Furthermore, in vitro studies have shown the effects of GSK3532795 to be additive when combined with other antiretrovirals, including integrase inhibitors (INIs). Different modes of action may be complementary as INIs act at an earlier point in the HIV-1 life cycle, by preventing viral cDNA integration into chromosomal DNA, and GSK3532795 works at a later point by preventing the maturation of HIV-1 particles. Because immature viruses do not go through a complete life cycle, it is conceivable that a 2-drug regimen using INIs and MIs could lead to a full regimen with good viral suppression and improved tolerability. Larger studies in HIV-1–infected patients would be needed to evaluate these hypotheses.

GSK3532795 was generally well tolerated, with no serious AEs or AEs leading to discontinuation. Bilirubin changes in part B were attributable to ATV and not GSK3532795. No clinically significant bilirubin increases were observed during GSK3532795 monotherapy.

Pharmacokinetics and exposure–response results support GSK3532795 QD dosing given the long $T_{1/2}$ (30–35 hours), the virologic response and suppression even after cessation of dosing, and low intersubject pharmacokinetic variability. GSK3532795 systemic exposures increased in proportion to dose across the 5–40 mg QD dose range and then increased less than proportional to dose for the 80 mg and 120 mg QD doses,

most likely due to the low solubility of GSK3532795 (<0.001 mg/mL in aqueous media), which limits absorption at increasing doses. Increased GSK3532795 exposures with ATV ± RTV and food, relative to monotherapy under fasted conditions, are likely due to a combination of increased absorption with food and CYP3A4 inhibition by ATV and RTV. The plateau in antiviral response observed at GSK3532795 C_{24} ≥500 ng/mL is consistent with protein-binding adjusted target C_{trough} of 643 ng/mL, representing plasma concentrations that are expected to provide coverage of >90% of subtype B viruses, which includes the ΔV370 genotype (the major polymorph found in non–subtype B viruses). GSK3532795 binds tightly and reversibly to HIV-1 Gag and has greater potency and lower human serum binding (86%) than BVM, resulting in a low EC_{50} shift in the presence of serum (5.4-fold), improved biopharmaceutical properties with low-dose prediction and a $T_{1/2}$ supportive of QD dosing, and coverage of naturally occurring Gag polymorphisms [25]. These properties, along with the dose-ranging data presented here, supported the further development of GSK3532795.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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