Pharmacodynamics, Safety, and Pharmacokinetics of BMS-663068, an Oral HIV-1 Attachment Inhibitor in HIV-1–Infected Subjects

Richard E. Nettles,1,a,b Dirk Schürmann,4,a Li Zhu,1 Michele Stonier,1 Shu-Pang Huang,1 Ih Chang,1 Caly Chien,1,b Mark Krystal,3 Megan Wind-Rotolo,1 Neelanjana Ray,1 George J. Hanna,1 Richard Bertz,1 and Dennis Grasela2

1Research and Development, Bristol-Myers Squibb (BMS), Princeton; 2Discovery Medicine and Clinical Pharmacology, BMS, Pennington, New Jersey; 3Research and Development, BMS, Wallingford, Connecticut; and 4Charité-Universitätsmedizin Berlin, Germany

Background. BMS-663068 is a prodrug of the small-molecule inhibitor BMS-626529, which inhibits human immunodeficiency virus type 1 (HIV-1) infection by binding to gp120 and interfering with the attachment of virus to CD4+ T-cells.

Methods. Fifty HIV-1–infected subjects were randomized to 1 of 5 regimen groups (600 mg BMS-663068 plus 100 mg ritonavir every 12 hours [Q12H], 1200 mg BMS-663068 plus 100 mg ritonavir every bedtime, 1200 mg BMS-663068 plus 100 mg ritonavir Q12H, 1200 mg BMS-663068 Q12H plus 100 mg ritonavir every morning, or 1200 mg BMS-663068 Q12H) for 8 days in this open-label, multiple-dose, parallel study. The study assessed the pharmacodynamics, pharmacokinetics, and safety of BMS-663068.

Results. The maximum median decrease in plasma HIV-1 RNA load from baseline ranged from 1.21 to 1.73 log10 copies/mL. Plasma concentrations of BMS-626529 were not associated with an antiviral response, while low baseline inhibitory concentrations and the minimum and average steady-state BMS-626529 plasma concentrations, when adjusted by the baseline protein binding–adjusted 90% inhibitory concentration (inhibitory quotient), were linked with antiviral response. BMS-663068 was generally well tolerated.

Conclusions. Administration of BMS-663068 for 8 days with or without ritonavir resulted in substantial declines in plasma HIV-1 RNA levels and was generally well tolerated. Longer-term clinical trials of BMS-663068 as part of combination antiretroviral therapy are warranted.

Clinical Trials Registration. NCT01009814.

The currently available antiretroviral drugs target various distinct steps in the human immunodeficiency virus type 1 (HIV-1) lifecycle; however, despite the large number of drugs available, there is a continued need for the development of novel drugs that target different stages of viral replication. This is due primarily to the development of resistance to existing compounds and the need for improvement in long-term safety, tolerability, and/or immunologic health over currently available antiretroviral agents [1, 2].

The replication cycle of HIV-1 is a complex and multistep process that initially involves the entry of the virus into host cells via attachment, coreceptor binding, and membrane fusion [3, 4]. These processes offer considerable potential for therapeutic intervention; indeed, some of the entry inhibitors currently approved for the treatment of HIV-1 target these steps in the lifecycle. Maraviroc prevents binding of HIV-1 to the coreceptor C-C chemokine receptor 5, while enfuvirtide is an injectable peptide that inhibits the...
gp41-mediated fusion of the host and viral cell membranes [5, 6].

HIV-1 attachment inhibitors represent a new class of entry inhibitors that prevent the initial interaction between virus and host cell by binding to the viral envelope protein gp120 and blocking attachment of the virus to the CD4 receptor on CD4+ T-cells. Proof of concept for this class was achieved with an earlier molecule, BMS-448043, in an 8-day monotherapy trial [7]. BMS-448043 was found to be generally safe and well tolerated. However, the development of this molecule was discontinued primarily because of its poor bioavailability and suboptimal pharmacokinetics.

BMS-663068 is a methyl phosphate prodrug of the attachment inhibitor BMS-626529. Compared with BMS-448043, BMS-626529 has increased potency against a range of viruses and a slower off-rate from purified envelope protein [8]. BMS-626529 exhibited a broad spectrum of antiviral activity against a panel of clinical isolates, with a 50% inhibitory concentration (IC50) ranging from subnanomolar levels to >0.1 µM [8]. There was a need for a prodrug with improved aqueous solubility because of the slow dissolution and limited rate and extent of absorption of the parent compound [9]. Administration of BMS-663068 to healthy volunteers in single-dose and multiple-ascending-dose studies showed rapid conversion to and absorption of the active form, BMS-626529 [10]. An extended-release formulation of BMS-663068 optimized the pharmacokinetics of BMS-626529 by decreasing the maximum plasma concentration and increasing trough plasma concentrations to enable once- or twice-daily dosing [10]. Coadministration of ritonavir was found to enhance the exposure to BMS-626529 in these subjects. On the basis of this finding, the current study incorporated ritonavir in the majority of regimen groups.

This 8-day monotherapy trial evaluated the antiviral activity, pharmacokinetics, and safety of BMS-626529, administered as BMS-663068 with or without ritonavir, in HIV-1–infected subjects. The study also evaluated measures of BMS-626529 exposure and baseline viral susceptibility as predictors of response to BMS-663068.

METHODS

Study Design

This study was a randomized, open-label, multiple-dose, parallel phase IIa study. Five dose regimens of BMS-663068 were evaluated for 8 days: group 1, 600 mg BMS-663068 plus 100 mg ritonavir every 12 hours (Q12H); group 2, 1200 mg BMS-663068 plus 100 mg ritonavir every bedtime (QHS); group 3, 1200 mg BMS-663068 plus 100 mg ritonavir Q12H; group 4, 1200 mg BMS-663068 Q12H plus 100 mg ritonavir every morning (QAM); and group 5, 1200 mg BMS-663068 Q12H. Subjects were admitted to a clinical facility between November 2009 and June 2010 and were confined to the clinical facility until day 11. Subjects returned to the unit on day 15 for a follow-up visit and on day 50 (±3 days) for discharge. All doses of study medication were administered under fed conditions. A standard breakfast meal (421 kcal, 16.7 g fat, 18.2 g protein) was administered prior to the morning dose, and an evening snack (approximately 300–350 kcal) was administered prior to the evening dose. Subjects were randomly assigned to a regimen according to a computer-generated randomization scheme and were stratified by prior antiretroviral treatment history.

Study Subjects

Eligible subjects were adults (aged ≥18 years) infected with subtype B HIV-1 who had plasma HIV-1 RNA levels ≥5000 copies/mL (Roche COBAS Amplicor) and CD4+ T-cell counts ≥200 cells/µL. Enrollment in this study was restricted to subtype B since limited data were available on the activity of BMS-663068 in non–subtype B HIV-1 strains at the time of enrollment. Subjects could be antiretroviral treatment naive (defined as no receipt of therapy for ≥1 week) or experienced; however, all antiretroviral therapy must have been discontinued for at least 8 weeks prior to participation in the study.

Prior exposure to HIV-1 attachment inhibitors was prohibited. In addition, the use of investigational drugs or placebo was prohibited, as was use of prescription medication within 4 weeks of study drug administration and the use of other drugs, including over-the-counter medications, within 1 week of study drug administration, unless approved by the investigator and study medical monitor. Subjects with clinically relevant deviations from normal findings of physical, electrocardiogram (ECG), and/or laboratory examinations were excluded, as were subjects with hepatitis B virus or hepatitis C virus coinfection. Women of childbearing potential were required to have a negative result of a serum or urine pregnancy test within 24 hours prior to receiving study medication.

All subjects provided written informed consent prior to participation in the study. The study was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The protocol was approved by the institutional review board at the study site.

Evaluations

Physical examinations, vital sign measurements, 12-lead ECGs, clinical laboratory tests, urine drug screening, pregnancy tests (for women), and blood sampling for HIV-1 RNA analysis and measurement of CD4+ and CD8+ T-cell counts were performed at screening (within 35 days prior to study enrollment) and at selected time points throughout the study. Plasma HIV-1 RNA load was measured at screening, on days 1–11, on day 15, and at discharge (day 50). Antiviral activity was assessed by the magnitude and rate of change in plasma HIV-1 RNA load from baseline (ie, before receipt of the dose
on day 1). Blood samples for measurement of CD4+ and CD8+ T-cell counts were obtained at screening; on days 1, 8, and 15; and at discharge. All blood samples obtained for measurement of plasma HIV-1 RNA load and CD4+ and CD8+ T-cell counts were collected prior to dosing, with the time of collection maintained throughout the inpatient portion of the study. Plasma samples for drug susceptibility testing were collected at screening; on days 1, 4, 8, and 15; and at discharge. Drug susceptibility (expressed as the IC_{50}) was assessed using the Phenosense® Entry Assay (Monogram Biosciences, San Francisco, CA).

**Pharmacokinetic Analysis**

Serial blood samples for pharmacokinetic analysis were collected on days 1 and 8–11. Plasma concentrations of BMS-626529 were determined by validated liquid chromatography and tandem mass spectrometry with a linear range of 5–5000 ng/mL. The between-run and within-run variabilities for the analytical quality control samples had coefficients of variation of ≤5.7% and ≤11.3%, respectively.

Pharmacokinetic parameters for BMS-626529 were derived from plasma concentration-versus-time data using a non-compartmental method. Maximum plasma concentration (C_{max}), trough plasma concentration (C_{min}), and area under the plasma concentration-time curve over a 24-hour period (AUC_{0–24h}) were reported. The average steady-state concentration (C_{ss,avg}) was calculated as AUC_{0–24h}/24. Plasma protein binding to BMS-626529 was determined using equilibrium dialysis. In addition, to directly compare in vivo BMS-626529 plasma concentrations with in vitro drug susceptibility, the measured in vitro IC_{50} values were transformed to a protein binding–adjusted 90% inhibitory concentration (PBA IC_{90}), using the following formula: PBA IC_{90} (ng/mL) = sc × mw × IC_{50} (μM)/fu, where sc is a factor that scales IC_{50} from IC_{50} (sc = 5.5), mw is the molecular weight of BMS-626529 free base (mw = 473.48 g/mole), and fu is the mean fraction of BMS-626529 free from protein binding (fu = 0.12). Inhibitory quotient (IQ) was defined as the ratio C_{ss,avg} or C_{min} of BMS-626529 to PBA IC_{90}.

**Statistical Analysis**

The primary objective of the study was to assess the antiviral activity of BMS-626529 following administration of selected regimens of BMS-663068 with and without ritonavir administered orally to HIV-1–infected subjects for 8 days. Secondary objectives included assessment of CD4+ and CD8+ T-cell counts and BMS-626529 pharmacokinetics, safety, and tolerability. The relationship between change in plasma HIV-1 RNA load on day 9 from baseline and measurements of BMS-626529 exposure (C_{max}, C_{min}, and C_{ss,avg}) and IQs were also assessed.

Antiviral activity was assessed on the basis of changes in log_{10} HIV-1 RNA levels from baseline, with descriptive statistics, including mean, standard error, median, and range, for each regimen group from day 2 to day 11 and at day 15. The maximum decline from baseline in log_{10} HIV-1 RNA levels over the study period was determined for each subject and was similarly summarized by regimen group. To explore the effect of prior antiretroviral treatment on the antiviral activity of BMS-626529, the change from baseline in log_{10} HIV-1 RNA load was further summarized by treatment regimen and prior antiretroviral treatment history (naive versus experienced). In addition, on the basis of the drug susceptibility of viruses at baseline, sensitivity analyses that excluded subjects for whom the IC_{50} was undetermined or above the assay’s upper limit were also performed, using similar descriptive statistics.

Pharmacokinetic exposure parameters of BMS–626529 (C_{max}, C_{min}, AUC_{0–24}, and C_{ss,avg}) were summarized by geometric mean, coefficient of variation, and range. The individual maximum viral load reductions were plotted versus exposure parameters or IQ to explore the relationship.

In addition to detailed individual listings, all adverse events (AEs) recorded during the study were listed and tabulated by regimen group, body system, and preferred term, and any significant abnormal vital signs, clinical laboratory results, ECG readings, and physical examination findings were summarized by regimen group.

**RESULTS**

**Subject Disposition and Baseline Characteristics**

Fifty subjects were randomly assigned to 1 of 5 regimen groups (Figure 1). A total of 48 subjects completed the study; 2 subjects were withdrawn because they did not meet the study inclusion criteria (both subjects were infected with non-subtype-B HIV-1) and discontinued treatment before the completion of the study. These subjects were included only in the pharmacokinetic and safety evaluations. Baseline demographic characteristics and disease characteristics were generally well balanced among the regimen groups (Table 1). Approximately 70% of subjects enrolled in the study were antiretroviral treatment naive; the median baseline plasma HIV-1 RNA level was 4.40 log_{10} copies/mL, and the median CD4+ T-cell count was 432 cells/μL.

Performance of a drug-susceptibility assay of viruses at baseline revealed baseline IC_{50} values that were greater than the assay’s upper limit (0.1 µM) in 2 subjects in group 1, in 1 subject in group 4, and in 4 subjects in group 5. Baseline IC_{50} values could not be obtained for 2 subjects because of assay failure.

*Antiviral Activity*

The mean change from baseline in the log_{10} plasma HIV-1 RNA level over time is shown in Figure 2A; data from subjects with IC_{50} values <0.1 µM are illustrated in Figure 2B. In general, increases in plasma HIV-1 RNA load were initially
observed on treatment days 2 and 3; however, mean decreases from baseline were subsequently observed during the treatment period and up to day 15 for all groups. The maximum change from baseline was observed between days 10 and 15 among the majority of subjects (the last day of dosing was on day 8), with plasma HIV-1 RNA levels returning to baseline levels by study discharge. The median maximum decrease in plasma HIV-1 RNA load from baseline over the whole study period ranged from 1.21 log10 copies/mL among subjects in group 5 to 1.73 log10 copies/mL for subjects in group 3 (Figure 3A). The lower response observed among subjects in group 5 was likely due to IC50 values >0.1 µM exhibited by 4 of 10 subjects in the group at baseline. Indeed, when these subjects were excluded, no clinically meaningful differences in plasma HIV-1 RNA suppression were observed (Figures 2B and 3B). In addition, there were no differences in antiviral activity observed when comparing treatment-naive and antiretroviral-experienced subjects across regimen groups, and on the basis of preliminary data analysis, there were no substantial changes in susceptibility over the course of the study (data not shown). Plasma HIV-1 RNA levels <400 copies/mL were observed among 18 of 48 subjects (38%) (group 1, n = 2; group 2, n = 2; group 3, n = 4; group 4, n = 6; and group 5, n = 4). None of the subjects with a baseline sensitivity >0.1 µM achieved plasma HIV-1 RNA levels <400 copies/mL.

Median increases in CD4+ T-cell counts from baseline were observed for all regimen groups on day 8 (group 1, 130 cells/µL; group 2, 86 cells/µL; group 3, 102 cells/µL; group 4, 38 cells/µL; and group 5, 23 cells/µL). No clinically relevant changes in CD8+ T-cell counts or the percentage of CD4+ and CD8+ T cells were observed.

**Pharmacokinetics**

The multiple-dose pharmacokinetics of BMS-626529 following administration of BMS-663068 with and without ritonavir are summarized in Table 2. Steady-state BMS-626529 exposures in subjects receiving BMS-663068 600 mg Q12H plus ritonavir 100 mg Q12H (group 1) or 1200 mg QHS plus ritonavir 100 mg QHS (group 2) had comparable AUC0–24 values but very different Cmin values, consistent with the Q12H versus QHS dosing frequency. Further, steady-state BMS-626529 exposures in subjects receiving BMS-663068 1200 mg Q12H plus ritonavir 100 mg Q12H (group 3) or 100 mg QAM (group 4) were modestly higher by 45%–51%, 30%–42%, and 17%–48% in Cmax, AUC0–24, and Cmin, respectively, compared with subjects receiving 1200 mg Q12H without ritonavir (group 5).

**Predictors of Antiviral Activity**

The relationship between antiviral activity and both baseline viral susceptibility (as measured by IC50) and BMS-626529
plasma concentrations (as measured by C_{\text{ss,avg}} and C_{\text{min}}) was assessed. A high variability in baseline IC_{50} was observed, with values ranging from 0.00002 to >0.1 µM; however, subjects were not stratified according to baseline IC_{50}. A high IC_{50} at baseline was associated with a weaker antiviral response, with the majority of subjects with a baseline IC_{50} >0.1 µM failing to achieve a >1 log_{10} reduction in HIV-1 RNA level (Figure 4).

Conversely, a low IC_{50} was associated with a more substantial antiviral response; all patients with a baseline IC_{50} <0.1 µM achieved a ≥1 log_{10} reduction in HIV-1 RNA load.

The individual maximum viral load reductions were plotted versus exposure parameters or IQ to explore the relationship, and those with the greatest association are illustrated in Figure 5. No associations were noted between either the change on day 9 or the maximum change in HIV-1 RNA levels from baseline and C_{\text{ss,avg}} and C_{\text{min}} with the doses tested in this study. However, IQs were associated with antiviral activity. The associations appeared to be similar whether the IQ was calculated on the basis of C_{\text{min}} or C_{\text{ss,avg}}. Scatter plots of viral load change from baseline at day 9 versus the IQ (C_{\text{min}}) or IQ (C_{\text{ss,avg}}) are shown in Figures 5A and 5B, respectively.

No evidence of a correlation between changes in CD4+ and CD8+ T-cell counts and baseline viral sensitivity, IQs, or pharmacokinetic parameters was observed (data not shown).

Safety
Overall, 39 subjects (78%) experienced ≥1 AE, and 33 (66%) experienced ≥1 treatment-related AE during the 50-day monitoring period. All AEs were considered to be mild or moderate in intensity (grade 1 or 2); no grade 3 or 4 AEs were reported. The most frequently reported treatment-related AEs were headache (in 16 subjects; 10 had grade 1 intensity), rash (in 8 subjects; 7 had grade 1 intensity), and micturition urgency (in 7 subjects; all had grade 1 intensity). No serious AEs or deaths were reported, and no subjects discontinued study medication because of an AE. There were no relevant differences in the type or frequency of AEs between the regimen groups. No clinically relevant changes in laboratory parameters, vital signs, ECGs, or physical examination findings were observed during the study.

**DISCUSSION**

BMS-663068 is the prodrug of a novel HIV-1 attachment inhibitor, BMS-626529, that targets the viral envelope protein gp120. The results of this study represent the first report of the antiviral activity and safety of BMS-663068 in HIV-1–infected subjects. Short-term dosing of BMS-663068 with or without ritonavir resulted in substantial declines in plasma HIV-1 RNA levels in both antiretroviral-naive and antiretroviral-experienced subjects, with all regimen groups experiencing a median drop in plasma HIV-1 RNA load of >1 log_{10} during...
the 8-day dosing period. Notably, if subjects with a baseline IC50 >0.1 µM were excluded from the analysis, all regimen groups achieved a median drop in plasma HIV-1 RNA load of >1.5 log10. Such a drop in viral load compares well with results of short-term monotherapy with other antiretrovirals. A median drop in viral load of >1.5 log10 has been observed with potent antiretrovirals that target HIV-1 reverse transcriptase, protease, integrase, and cell entry [11, 12]. Plasma HIV-1 RNA level generally increased on days 2 and 3 of treatment before dropping for the remainder of the dosing interval and for several days thereafter in many subjects. The etiology for these observations is unknown but is possibly associated with the unique mechanism of action of an attachment inhibitor that binds to the gp120 molecule and does not allow the virus to bind to host cells, thereby resulting in an initial increase of circulating HIV-1 virions detectable in the plasma.

In this study, BMS-663068 appeared to be generally well tolerated. Although a majority of subjects experienced an AE over the 50-day monitoring period, the majority of AEs were mild, and none necessitated study drug discontinuation. The safety profile of BMS-663068 in this study was consistent with the profile reported in previous studies involving healthy volunteers [10]. Larger comparative, controlled studies will be required to better define the safety and tolerability of BMS-663068.

Increases in median absolute CD4+ T-cell counts were observed during short-term dosing of BMS-663068 in this study.
However, the clinical relevance of these findings is unclear because of the small number of subjects in each group and the short duration of treatment in this study. Potential benefits associated with attachment inhibitors (due to the unique effect of this novel mechanism of action, which prevents the initial interaction between virus and host cell), particularly with regard to immune restoration and the amelioration of inflammation and cellular activation, will be defined in longer-term clinical trials.

BMS-626529 has favorable pharmacokinetics following administration of the prodrug BMS-663068. Developed as an extended-release tablet, the current formulation has led to a lower $C_{\text{max}}$ and higher $C_{\text{min}}$ of BMS-626529, compared that with the immediate-release capsule [10]. Coadministration of ritonavir led to only modest increases in drug exposure, with no notable gain in plasma HIV-1 RNA load drop. In subjects with susceptible virus (<0.1 $\mu$M), all 5 regimen groups had similar antiviral efficacy (Figure 3B). These findings support the further investigation of lower doses of BMS-663068 given without ritonavir in subjects with susceptible virus at baseline.

Drug susceptibility of viruses at baseline has previously been shown to be an important determinant of viral response with this class of drug [7]. Similarly, the analysis of predictors of antiviral response in this study demonstrated that subjects with an $IC_{50}>0.1$ $\mu$M to BMS-626529 demonstrated a weak antiviral response (a majority of subjects did not achieve a $<1 \log_{10}$ decline in plasma HIV-1 RNA load). Seven subjects (14%) in this study had a baseline $IC_{50}>0.1$ $\mu$M, including 4 subjects randomized to group 5. Exclusion of subjects either with a baseline $IC_{50}>0.1$ $\mu$M or with missing values led to an

---

Figure 3.  
A, Median maximal change in plasma human immunodeficiency virus type 1 (HIV-1) RNA load from baseline.  
B, Median maximal change in plasma HIV-1 RNA load from baseline, excluding subjects with a missing baseline 50% inhibitory concentration ($IC_{50}$) or a baseline $IC_{50}>0.1$ $\mu$M. Ineligible subjects ($n=2$) are excluded from both analyses. Abbreviations: QAM, every morning; QHS, every bedtime; Q12H, every 12 h; RTV, ritonavir.
increase in the median maximum change in plasma HIV-1 RNA load (−1.60 vs −1.21 log₁₀ copies/mL) for this group, indicating the importance of considering baseline viral susceptibility in future studies. IQs based on \( C_{\text{min}} \) and \( C_{\text{avg}} \) were also found to be associated with antiviral activity, and the associations appeared to be similar whether the IQ was calculated on the basis of \( C_{\text{min}} \) or \( C_{\text{avg}} \). Pharmacokinetic exposures (ie, plasma \( C_{\text{avg}} \) and \( C_{\text{min}} \)) alone were not predictive of response in the dose range studied. Of interest, one subject with a high baseline IC₅₀ (approximately 6.6 µM) responded well during the course of the study, with a maximum viral load change of −1.61 log₁₀. It is not clear why this subject responded well, but virus from this subject and from all other subjects with high baseline IC₅₀ values will be examined to understand the correlates of in vitro sensitivity to the active agent. A broad range of IC₅₀ values (52 pM to >0.1 µM) has been observed.

### Table 2. Summary Statistics for BMS-662529 Pharmacokinetic Parameters on Day 8 After Administration of BMS-663068

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1: 600 mg Q12H + RTV 100 mg Q12H (n=9)</th>
<th>Group 2: 1200 mg QHS + RTV 100 mg QHS (n=9)</th>
<th>Group 3: 1200 mg Q12H + RTV 100 mg Q12H (n=10)</th>
<th>Group 4: 1200 mg Q12H + RTV 100 mg QAM (n=10)</th>
<th>Group 5: 1200 mg Q12H (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ), µg/mL (^a)</td>
<td>2.24 (1.30–4.08); 43.3</td>
<td>3.47 (2.08–5.31); 31.7</td>
<td>5.05 (3.12–7.30); 31.7</td>
<td>4.93 (2.25–8.79); 40.1</td>
<td>3.39 (2.38–4.06); 15.9</td>
</tr>
<tr>
<td>( C_{\text{min}} ), µg/mL (^b)</td>
<td>0.411 (0.170–1.08); 78.2</td>
<td>0.0545 (0.0139–0.237); 138</td>
<td>0.772 (0.386–1.69); 59.5</td>
<td>0.613 (0.214–1.73); 65.9</td>
<td>0.524 (0.217–1.25); 59.0</td>
</tr>
<tr>
<td>AUC₀–2₄h, µg·h/mL</td>
<td>26.8 (12.3–54.9); 56.1</td>
<td>23.0 (12.6–44.2); 48.2</td>
<td>60.6 (34.7–87.2); 30.6</td>
<td>55.1 (22.5–97.6); 44.3</td>
<td>42.6 (31.1–55.6); 21.5</td>
</tr>
</tbody>
</table>

Data are geometric means (range); coefficient of variation.

Abbreviations: AUC₀–2₄h, area under the concentration-time curve over a 24-hour period; \( C_{\text{max}} \), maximum concentration; \( C_{\text{min}} \), minimum concentration; QAM, every morning; QHS, every evening; Q12H, every 12 h; RTV, ritonavir.

\(^a\)For twice-daily doses, morning and evening \( C_{\text{max}} \) values were used to calculate geometric means.

\(^b\)For twice-daily doses, concentrations at predose, 12 h after the morning dose, and 12 h after the evening dose were used to calculate geometric means. For daily doses, concentrations at predose and 24 h were used to calculate geometric means.

---

![Figure 4](image-url)

**Figure 4.** Fifty percent inhibitory concentration (IC₅₀) as a potential predictor of the plasma human immunodeficiency virus type 1 (HIV-1) RNA response. \(^a\)Phenosense® Entry Assay (Monogram Biosciences): upper limit of quantitation = 0.1 µM. Abbreviations: QAM, every morning; QHS, every bedtime; Q12H, every 12 h; RTV, ritonavir.
for BMS-626529, with most viruses having a low IC50, resulting in the potential for high IQs in the majority of subjects. For instance, in vitro studies with 133 subtype B clinical envelopes examined for susceptibility to BMS-626529 showed that 73% of the isolates exhibited an IC50 <0.001 μM, while ≥98% exhibited an IC50 <0.1 μM [8]. Lower numbers of clinical isolates of subtype A (33) and subtype C (36) showed similar results, with ≥88% and ≥94%, respectively, exhibiting an IC50

Figure 5. Change in the log10 plasma human immunodeficiency virus type 1 (HIV-1) RNA level from baseline at day 9 versus A, the ratio of the minimum plasma concentration (Cmin) to the baseline protein binding–adjusted 90% inhibitory concentration (PBA IC90; Pearson correlation, −0.4869 [P = .0006]) and the B, ratio of the average steady-state concentration (Css,avg) to the baseline PBA IC90 (Pearson correlation, −0.4731 [P = .0009]). Open symbols = subjects with baseline 50% inhibitory concentration >1 μM. Abbreviations: IQ, inhibitory quotient; QAM, every morning; QHS, every bedtime; Q12H, every 12 h; RTV, ritonavir.
anticipated that a large percentage of the HIV-1 subtype B virus would be highly susceptible to BMS-663068. Nevertheless, it is anticipated that a large percentage of the HIV-1-infected population would be highly susceptible to BMS-663068.

This proof-of-concept study demonstrates the potent antiviral activity of the novel attachment inhibitor prodrug BMS-663068 in HIV-1-infected subjects. These data, together with the favorable pharmacokinetic profile and generally good tolerability observed in this study, support the further clinical development of BMS-663068 in combination antiretroviral therapy. A phase IIb study of BMS-663068 in treatment-experienced subjects (NCT01384734) is currently ongoing.

Notes

Acknowledgments. We thank the Bristol-Myers Squibb employees Susan Lubin, for operational management of the study, and Yaoshi Wu, for statistical support. Coordination of the study was also provided by Sabine Franck and Nadine Lichtenberg (Parexel International GmbH). We also thank the following SGS employees: Cindy Van Sande (Clinical Research), Ann De Laet (Biometrics), Joachim Dejonckheere (Statistics), Jan Vermeir (Coordination of Medical Writing), Koen Jolling (Pharmacokinetics), Zuzanne Kwade (Medical Affairs), and Bruno Speder (Regulatory Affairs). Finally, we thank the subjects involved in the study. Editorial assistance was provided by Andrew Street of MediTech Media and was funded by Bristol-Myers Squibb.

Financial support. This work was supported by Bristol-Myers Squibb.

Potential conflicts of interest. R. E. N. has stock/stock options in Bristol-Myers Squibb. L. Z., S.-P. H., M. K., M. W.-R., G. J. H., R. B., I. C., and D. G. are employees of and have stock/stock options in Bristol-Myers Squibb. N. R. and M. S. are employees of Bristol-Myers Squibb. D. S. has served as a consultant to Bristol-Myers Squibb and has received money for his institution. C. C. certifies no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References