

Randomized Placebo-Controlled Study of the Safety, Tolerability, Antiviral Activity, and Pharmacokinetics of 10-Day Monotherapy With BMS-986001, a Novel HIV NRTI, in Treatment-Experienced HIV-1–Infected Subjects

Laurent Cotte, MD,* Pierre Dellamonica, MD,† Francois Raffi, MD, PhD,‡
 Yazdan Yazdanpanah, MD, PhD,§ Jean-Michel Molina, MD,|| François Boué, MD,¶ Yasuo Urata, MSc,#
 H. Phyllis Chan, PhD,** Li Zhu, PhD,** Ih Chang, PhD,** Richard Bertz, PhD,**
 George J. Hanna, MD,** Dennis M. Grasela, PharmD, PhD,** and Carey Hwang, MD, PhD**

Objective: To investigate the safety, tolerability, pharmacokinetics, and antiviral activity of BMS-986001 (a nucleoside reverse transcriptase inhibitor) in treatment-experienced, HIV-1–infected subjects not exposed to antiretroviral treatment in the previous 3 months.

Methods: Thirty-two HIV-1–infected subjects were randomized (3:1) to receive BMS-986001 or placebo once daily for 10 days in this double-blind, placebo-controlled, dose-escalating monotherapy phase IIa study. There were 4 treatment groups (100, 200, 300, and 600 mg, all once daily) of 8 subjects each (BMS-986001, n = 6/placebo n = 2).

Results: BMS-986001 was generally well tolerated, with no discontinuations due to adverse events and no deaths occurring. Adverse events were experienced by 22 of 24 BMS-986001-treated subjects and did not seem to be dose related. The majority were mild and considered unrelated or unlikely to be related to the study drug. The pharmacokinetics of BMS-986001 were dose proportional. Median decrease in plasma HIV-1 RNA from baseline to day 11 was 0.97, 1.15, 1.28, and 1.15 log₁₀ copies/mL for BMS-986001 at 100, 200, 300, and 600 mg, respectively. Plasma area under the curve correlated with the antiviral activity of BMS-986001, indicating that area under the curves produced by 100–600 mg doses were on the upper end of the exposure–response curve. One subject with a single thymidine analog mutation at baseline responded well to BMS-986001.

Conclusions: Administration of BMS-986001 for 10 days resulted in substantial decreases in plasma HIV-1 RNA levels for all dose groups and was generally well tolerated. These data support continued clinical development of BMS-986001 at a dose of 100 mg, once daily or greater.

Trial registration: EUDRACT Number 2008-004810-29.

Key Words: HIV type 1, nucleoside reverse transcriptase inhibitor, BMS-986001, antiviral activity, pharmacokinetics, safety

(*J Acquir Immune Defic Syndr* 2013;63:346–354)

Received for publication December 7, 2012; accepted April 9, 2013.

From the *Service d'hépatologie et de sida, Hôtel-Dieu, Hospices Civils de Lyon and INSERM U1052, Lyon, France; †Service d'inféctiologie, Université de Nice Sophia Antipolis and CHU, Nice, France; ‡University of Nantes, Nantes, France; §Service Universitaire des Maladies Infectieuses et du Voyageur, Centre Hospitalier de Tourcoing, Tourcoing, France; ||Department of Infectious Diseases, Hôpital Saint-Louis, AP-HP and INSERM U941, University of Paris Sorbonne Cité, Paris, France; ¶Hôpital Antoine Beclère, Paris, France; #Oncolys BioPharma, Tokyo, Japan; and **Bristol-Myers Squibb, Research and Development, Princeton, NJ.

Supported by Oncolys Pharma and Bristol-Myers Squibb. The authors had full access to all the data and take full responsibility for the accuracy of the data analysis. The authors received no financial support or compensation for this publication.

Presented in part at the 50th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, MA, September 12–15, 2010 (Abstract H-933) and at the 13th International Workshop on Clinical Pharmacology of HIV Therapy, Barcelona, Spain, April 16–18, 2012 (poster O_06).

F.R. has received research funding or honoraria from, or consulted for, Abbott, Avexa, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck & Co., Pfizer, Roche, and ViiV Healthcare; Y.Y. has received travel grants, honoraria for presentations at workshops, and consultancy honoraria from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead, Merck, Roche, Tibotec, and ViiV Healthcare. H.P.C., L.Z., I.C., R.B., G.J.H., D.M.G., and C.H. are employees of Bristol-Myers Squibb.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Carey Hwang, MD, PhD, Bristol-Myers Squibb, Research and Development, PO Box 5400, Princeton, NJ 08543-5400 (e-mail: carey.hwang@bms.com).

Copyright © 2013 by Lippincott Williams & Wilkins

INTRODUCTION

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) remain a cornerstone of combination antiretroviral therapy (cART) for HIV. Current treatment guidelines recommend that cART regimens for treatment-naïve patients consist of 2 NRTIs plus 1 other active agent, a non-NRTI, a protease inhibitor or an integrase inhibitor.¹ Despite the number of NRTIs available, and their wide use, there are ongoing concerns regarding the established and potential long-term toxicities of the class. Well-established toxicities include anemia [zidovudine (AZT)], pancreatitis [didanosine (ddI)], and other issues related to mitochondrial toxicity, including peripheral neuropathy [ddI and stavudine (d4T)], lipatrophy (d4T and AZT), and metabolic acidosis (mostly with d4T, ddI, and AZT).¹ As a result of these toxicities,

many NRTIs are now only used under special circumstances.¹ Lamivudine (3TC) and emtricitabine (FTC) have a favorable safety profile but cannot be used together because of a shared mechanism of action and a similar resistance profile. Major HIV-1 treatment guidelines currently recommend combinations of tenofovir disoproxil fumarate (TDF) or abacavir (ABC) with FTC or 3TC as part of initial HIV-1 treatment regimens.¹⁻³ ABC is not always preferred because it is associated with hypersensitivity reaction, and there is conflicting evidence regarding its effect on cardiovascular risk.^{1,3-6} Although TDF is preferred because of favorable tolerability and efficacy profile, concerns regarding nephrotoxicity decreased bone mineral density and increased risk of fractures remain.^{1,7,8}

The life expectancy for HIV-infected individuals has increased notably in the last decade,⁹ resulting in a population of increasing age and disease chronicity. This, together with the earlier start of cART treatment recommended by clinical guidelines,¹ means that many patients receive antiretroviral therapies for increasingly long durations.

The aforementioned concerns highlight a need for novel NRTIs with potent anti-HIV-1 activity, a good tolerability profile (similar or better than currently available antiretroviral agents), long-term safety (in terms of bone mineral density loss/decline in renal function), and limited cross-resistance to existing NRTIs. Furthermore, a convenient regimen to improve adherence (eg, once daily dosing or fixed dose combinations) is an increasingly important factor in the development of new NRTIs. Thus, pharmacokinetic (PK) profile and drug metabolism are important considerations.

BMS-986001 is a thymidine NRTI that has been developed to maintain the *in vitro* antiviral activity demonstrated by other NRTIs without the associated toxicity concerns. BMS-986001 is a novel analog of d4T, which, in preliminary *in vitro* experiments, demonstrated potent antiviral activity and reduced mitochondrial toxicity compared with d4T.¹⁰ It displayed reduced inhibition of host DNA polymerases compared with other thymidine analogs,¹¹ and there was evidence of a higher genetic barrier to resistance than its progenitor d4T.¹² Furthermore, BMS-986001 has demonstrated activity against a number of HIV-1 subtypes (Bristol-Myers Squibb, unpublished data, 2011) and against HIV-1 isolates with certain NRTI-associated mutations, such as K65R, L74V, and Q151M mutations.¹³ Viruses with thymidine analog mutations (TAMs) conferring reduced susceptibility to BMS-986001 were generally cross-resistant to many other NRTIs (Bristol-Myers Squibb, unpublished data, 2011). M184V induced low-level fold change (2- to 3-fold) in susceptibility to BMS-986001.^{12,13}

The safety, tolerability, PK, and pharmacodynamic effects of BMS-986001 were evaluated in a 10-day monotherapy trial in treatment-experienced HIV-1-infected subjects who were not exposed to any antiretroviral treatment in the previous 3 months.

METHODS

Study Design

A randomized, double-blind, placebo-controlled, dose-escalating, 10-day monotherapy study was conducted in treatment-experienced HIV-1-infected subjects at 6 centers in

France between December 2008 and September 2009. Four treatment groups (100, 200, 300, and 600 mg, all once daily) of 8 subjects each were enrolled. Within each group, subjects were randomized by a computer-generated randomization scheme (3:1 ratio) to receive BMS-986001 or placebo once daily for 10 days (BMS-986001, *n* = 6/placebo, *n* = 2). An independent Data Safety Monitoring Board was responsible for authorization of dose escalation and met 3 times during the study, once after each of the 100-, 200-, and 300-mg groups had completed treatment. A screened subject was included once and received 1 dose level. Study drug was administered as a single dose in the morning under fasting conditions. No food was allowed until 1 hour postdose. Doses were administered in the clinic on days 1, 2, 3, 5, and 10 and at home on the remaining days. Treatment allocation was performed by CRID Pharma according to a randomization list provided by the Contract Research Organization that remained blinded until database lock. There were 2 protocol amendments, one to test total cholesterol, low-density lipoprotein (LDL), gamma-glutamyl transpeptidase (γ GTP), and triglycerides in the fasting state, and the other for amylase testing. The study protocol, its amendments, and informed consent documents were approved by the French Regulatory Authority (AFSSAPS) and by the independent ethics committee of the coordinating center in Lyon, France. Written informed consent was obtained from all participants. The studies were performed in accordance with International Conference on Harmonization Good Clinical Practice guidelines.

Study Population

Subjects underwent screening evaluations up to 21 days before administration of study medication. Eligible subjects were HIV-1-infected adults, male or female (aged 18–60 years), with plasma HIV-1 RNA ≥ 5000 copies/mL (using standard approved HIV-1 RNA assays) and CD4⁺ T-cell counts ≥ 250 cells/mL stable within 3–6 months. Subjects were antiretroviral experienced but with no antiretroviral therapy within 3 months before screening and no indication for antiretroviral therapy according to guidelines at the time of the study.¹⁴ Concomitant therapy with nucleoside analogs and antiretroviral agents other than BMS-986001 was prohibited. Subjects did not receive concomitant therapy (prescription, over-the-counter or herbal) for the treatment of specific clinical events, unless prescribed by the investigator. Exclusion criteria were hepatitis B or C co-infection, history of hepatic or abnormal liver function tests (defined as $\geq 2.5 \times$ upper limit of normal), renal disease, or calculated creatinine clearance ≤ 80 mL/min (calculated using Cockcroft–Gault¹⁵) at screening or history of significant hematologic disease.

Evaluations

Safety and Tolerability

Adverse events (AEs) were recorded throughout. Clinical laboratory evaluations (hematology, blood chemistry, and urinalysis) were performed at screening and on days 1, 3, 5, 11, 17, and 24. Echocardiograms (ECGs) were performed at screening and on days 1 (predose and 2 hours postdose)

and 10 (2 hours postdose). Physical examinations and measurement of vital signs were performed at screening and on days 1, 5, 10, 12 (physical examination only), 17, and 24.

Antiviral Activity

Plasma HIV-1 RNA level was determined at screening and on days 1 (predose), 3, 5, 11, 17, and 24. CD4⁺ T-cell count was determined at screening and on days 1 (predose), 11, and 24.

Pharmacokinetics

Blood samples for PK analysis were collected predose and at 1, 2, 4, 9, 12, and 24 hours postdose on days 1 and 10. Samples were also collected predose on days 3 and 5 and on day 11 for analysis of trough concentration and on the morning of day 12. BMS-986001 concentration was assayed by validated liquid chromatography dual mass spectrometry. The lower limit of quantification for BMS-986001 was 1.00 ng/mL with overall coefficient of variance $\leq 8.1\%$. PK variables assessed included maximum observed plasma concentration (C_{\max}), time to C_{\max} (T_{\max}), area under the concentration-time curve in 1 dosing interval (AUC_{τ}), terminal plasma half-life after the last dose administered ($T_{1/2}$), and apparent total body clearance ($CL_{T/F}$) in the fasted state. The PK parameters of BMS-986001 were derived from the plasma concentration-time profiles via noncompartmental methods using WinNonlin (version 5.0; Mountain View, CA). Actual sampling times were used for the analysis.

Resistance Analysis

HIV-1 drug resistance genotype was assessed on days 1 (predose), 11, and 17 using standard, commercially available testing procedures. This assay did not cover the reverse transcriptase connection or RNase H domains. Genotype data on subjects before enrollment in the study are not available. Resistance analysis was performed at Monogram Biosciences (San Francisco, CA).

Statistical Analysis

The primary objective was to evaluate the safety and tolerability of BMS-986001. The secondary objectives were to assess the PK profile of multiple doses of BMS-986001, evaluate the antiviral activity of BMS-986001 compared with placebo (change from baseline in plasma HIV-1 RNA levels), and evaluate the resistance profile of BMS-986001.

A sample size of 6 subjects in each dose group resulted in $\geq 80\%$ probability of observing ≥ 1 occurrence of an event with underlying rate of $\geq 24\%$ at a given dose level and $\geq 80\%$ probability of observing a median HIV-1 RNA decrease of $\geq 0.8 \log_{10}$ at a given dose level if the true rate of achieving such decrease is at least 60%. The statistical analysis was performed using the SAS software for Windows, version 9.2 (SAS Institute Inc., Cary, NC). Safety analysis dataset: all subjects who received ≥ 1 dose of study drug; PK analysis dataset: all subjects who received ≥ 1 of study drug and provided evaluable plasma concentration versus time profiles.

AEs were classified as pretreatment (onset date/time before date/time of the first study medication) or treatment-emergent (onset date/time on or after date/time of the first

study medication). Frequency distribution of subjects with AEs was provided by treatment and coded according to MedDRA version 12.0, using preferred term and corresponding system organ class. The maximal severity grade and relationship to study drug was assessed by the investigator. Summary statistics were provided for vital signs, ECGs, and safety laboratory assessment data.

A descriptive analysis of plasma concentration at each time point and PK parameters of BMS-986001 on days 1 and 10 was performed. Individually, for days 1 and 10, statistical testing of dose proportionality of BMS-986001 in plasma for AUC_{τ} and C_{\max} was performed using the power model of Gough et al.¹⁶ A mixed model, using PROC MIXED in SAS, was computed with the natural log-transformed PK parameter as a dependent variable and the natural log-transformed dose as a fixed effect. Within this model, the 90% confidence interval (CI) on the slope was calculated. Dose proportionality was concluded if the 90% CI for the slope estimate was completely contained within the range 0.8 to 1.25.

Summary statistics by treatment and time point were provided for CD4⁺ T-cell counts and \log_{10} -transformed plasma HIV-1 RNA levels. Baseline was defined as measurements obtained predose on day 1. Exploratory analysis of changes from baseline was conducted to compare each dose with placebo using Mann-Whitney *U* test. Exploratory analysis of Spearman rank correlation coefficients between dose level and difference from baseline in plasma HIV-1 RNA and CD4⁺ T-cell counts at day 11 was performed.

An exposure-response analysis was performed to explore the relationship between AUC_{τ} on day 10 for BMS-986001 and day 11 change from baseline in \log_{10} plasma HIV-1 RNA levels. Nonlinear regression modeling was performed using WinNonlin. Data on HIV-drug resistance genotype were listed for subjects with any change from baseline.

RESULTS

Subject Disposition

A total of 32 subjects (median time since diagnosis, 12.0 years) were randomized and received study drug. All subjects were previously treated with NRTIs (see **Table S1, Supplemental Digital Content**, <http://links.lww.com/QAI/A424>, which shows previous instances of NRTI treatment at baseline). Baseline demographics and disease characteristics were generally well balanced between groups (Table 1). At baseline, median plasma HIV-1 viral RNA ranged from 4.0 to 4.8 \log_{10} copies/mL and median CD4⁺ T-cell count from 306.5 to 572.0 cells/ μ L. No subject received prohibited concomitant therapy. All 32 subjects were included in the safety and antiviral activity assessment groups. Two subjects were excluded from the PK data sets: one who did not receive study drug on day 10 was excluded from the day 10 summary and one who received the incorrect dose on day 1 was excluded from the day 1 summary.

Safety and Tolerability

A summary of AEs is presented in Table 2. A total of 27 (84%) subjects reported 95 treatment-emergent AEs

TABLE 1. Baseline Characteristics

| | 100 mg (n = 6) | 200 mg (n = 6) | 300 mg (n = 6) | 600 mg (n = 6) | Placebo (n = 8) |
|--|------------------|----------------|----------------|------------------|-----------------|
| Male, n (%) | 6 (100) | 6 (100) | 4 (66.7) | 5 (83.3) | 5 (62.5) |
| Age, median (min, max), y | 43.5 (38, 67) | 49 (35, 56) | 41.5 (26, 45) | 42 (26, 45) | 43.5 (35, 66) |
| Time since initial HIV diagnosis, median (min, max), y | 9 (3, 21) | 14.5 (2, 21) | 9 (2, 15) | 11 (7, 24) | 17 (8, 25) |
| No. antiretrovirals to which previously exposed, median (min, max) | 5 (2, 9) | 3.5 (2, 12) | 3 (2, 11) | 5.5 (2, 9) | 3 (1, 8) |
| Plasma HIV-1 RNA, median (min, max), log ₁₀ copies/mL* | 4.6 (3.8, 4.8) | 4.8 (3.5, 5.1) | 4.3 (3.9, 5.3) | 4.3 (3.5, 5.2) | 4.0 (3.6, 4.9) |
| CD4 ⁺ T-cells, median (min, max), cells/μL* | 306.5 (209, 588) | 349 (250, 472) | 572 (250, 854) | 383.5 (193, 765) | 371 (271, 538) |

*Data provided for HIV-1 RNA and CD4⁺ T-cell data are at screening. At baseline, HIV-1 RNA was below the minimum value at screening in 2 subjects (1 from the 100-mg group and 1 from the 600-mg group). The subject in the 100-mg dose group had a predose HIV-1 RNA level of 3650 copies/mL, and the subject in the 600-mg dose group had a predose HIV-1 RNA level of 307 copies/mL.

[82 (86.3%) grade 1; 11 (11.6%) grade 2; 2 (2.1%) grade 3], of which 30 were considered possibly study drug related, 7 unlikely to be related to study drug, and 58 unrelated to study drug (as assessed by the investigator). A greater proportion of BMS-986001–treated subjects reported grade 2 and 3 AEs [6/24 (25%)] compared with placebo [1/8 (12%)]; subjects may have experienced more than 1 AE. There were no grade 4 events. The median time between first dose and AE occurrence was 9 (0–23) days and 7 (0–23) days for subjects receiving BMS-986001 and placebo, respectively. AEs reported by subjects receiving BMS-986001 did not seem to be dose related; however, small subject numbers must be taken into consideration. The most common AEs (>10% of subjects) in the BMS-986001 treatment groups were abdominal pain (n = 5), lymphadenopathy (n = 4), nausea (n = 3), headache (n = 3), and fatigue (n = 3). In the placebo group, the most common AEs were nausea (n = 2) and increased blood lactic acid (n = 2).

The majority of AEs resolved before study discharge. One AE of grade 3 anxiety (100-mg group) and 1 AE of grade

1 fatigue (300-mg group) were unresolved at study discharge and were considered to be related to the study drug. The subject with grade 3 anxiety had a history of anxiety and also experienced grade 3 paranoia.

Two subjects in the 600-mg group each reported 1 serious AE, neither considered study drug related; streptococcal septicemia and cytomegalovirus primary infection. Three subjects experienced a grade 3/4 laboratory abnormality, none of which required intervention; decreased platelets (100-mg group), elevated serum potassium (200-mg group), and elevated LDL (placebo). The abnormality of decreased platelets occurred on day 17 (4.5-fold decrease from day 11) and returned to normal on day 24. There were no changes in other hematologic values for this subject; the decrease in platelets was probably because of platelet clumping. Elevated serum potassium (6.9 mEq/L) occurred on day 1 before dosing and returned to normal (4.3 mEq/L) on day 3. The elevation in LDL cholesterol was present at screening and remained elevated throughout. There were no clinically important ECG, vital sign, and other lipid or physical examination changes during follow-up.

TABLE 2. Summary of Treatment-Emergent Adverse Events

| Patients, n (%) | 100 mg (n = 6) | 200 mg (n = 6) | 300 mg (n = 6) | 600 mg (n = 6) | Placebo (n = 8) |
|--|----------------|----------------|----------------|----------------|-----------------|
| AE, n (%) | 5 (83.3) | 5 (83.3) | 6 (100.0) | 6 (100.0) | 5 (62.5) |
| Deaths, n (%) | 0 | 0 | 0 | 0 | 0 |
| ≥1 serious AE, n (%) | 0 | 0 | 0 | 2 (33.3) | 0 |
| Discontinuations due to AE(s), n (%) | 0 | 0 | 0 | 0 | 0 |
| Treatment-related AEs, n (%) | 4 (66.7) | 2 (33.3) | 5 (83.3) | 1 (16.7) | 4 (50.0) |
| Grade 2/3 AE, n (%)* | 2 (33.3) | 2 (33.3) | 0 | 2 (33.3) | 1 (12.5) |
| AEs occurring in ≥2 subjects in any BMS-986001 treatment group | | | | | |
| Headache | 0 | 0 | 3 (50.0) | 0 | 1 (12.5) |
| Nausea | 0 | 0 | 2 (33.3) | 1 (16.7) | 2 (25.0) |
| Lymphadenopathy | 0 | 2 (33.3) | 1 (16.7) | 1 (16.7) | 0 |
| Fatigue | 0 | 0 | 2 (33.3) | 1 (16.7) | 0 |
| Diarrhea | 0 | 1 (16.7) | 0 | 2 (33.3) | 0 |
| Presbyopia | 0 | 2 (33.3) | 0 | 1 (16.7) | 0 |
| Nightmare | 2 (33.3) | 0 | 0 | 0 | 0 |

*Abdominal pain, aerophagia, diarrhea, presbyopia, precordial pain, aspartate aminotransferase increased, presyncope, exacerbation of anxiety, paranoia, and hyperkeratosis were experienced by BMS-986001–treated subjects. Subjects may have experienced more than 1 AE. Headache was experienced by the placebo-treated subject.

Pharmacokinetics

Individual PK parameters for BMS-986001 are summarized by treatment in Table 3. At all doses, BMS-986001 was rapidly absorbed; maximum plasma BMS-986001 concentration was observed approximately 1–2 hours postdose in all groups. PK parameters were similar on days 1 and 10. There was no significant accumulation at any of the doses studied. The increase in exposure for C_{max} and AUC_{tau} to BMS-986001 over the dose range of 100–600 mg once daily for 10 days was dose proportional based on the power model: slope estimate (90% CI) for AUC_{tau} at day 10 = 1.025 (0.913 to 1.137) and C_{max} at day 10 = 0.986 (0.844 to 1.129).

Antiviral Activity

At day 11, the median decrease in plasma HIV-1 RNA levels was 1.20 \log_{10} , for all BMS-986001 doses combined (Fig. 1A). By day 11, the median (range) decrease was 0.97 (1.3 to -0.2), 1.15 (1.3 to 0.4), 1.28 (1.6 to 1.2), 1.15 (1.9 to -0.1), and 0.11 (0.3 to -0.2) \log_{10} copies/mL for BMS-986001 treatment groups 100, 200, 300, and 600 mg and placebo, respectively (see **Figure S1, Supplemental Digital Content**, <http://links.lww.com/QAI/A424>, for median change in plasma HIV-1 RNA level over time according to treatment group). Individual response variability was observed (Fig. 1B). Three subjects had decreased or no response (defined as $<0.5 \log_{10}$ copies/mL decline in plasma HIV-1 RNA by day 11) to BMS-986001. These 3 subjects had no NRTI-associated resistance mutations (including TAMs) at baseline. Previous treatments for each of the 3 patients were as follows—subject 1: AZT, 3TC, lopinavir/ritonavir, TDF/FTC, and atazanavir/ritonavir; subject 2: AZT, ddC, indinavir, and nevirapine; and subject 3: AZT and 3TC. Two of these 3 subjects had predose HIV-1 RNA <5000 copies/mL (3650 copies/mL for subject 1 and 307 copies/mL for subject 3).

Increases from baseline in median CD4⁺ T-cell counts were recorded in all BMS-986001 groups at day 11 (71.00–178.50 cells/ μ L) and all BMS-986001 groups except for the

600-mg group at day 24 (-20.00 to 145.50 cells/ μ L) (Fig. 2A). There was considerable variability in individual CD4⁺ T-cell response (Fig. 2B).

Exposure–Response Analysis

The exposure–response relationship between BMS-986001 steady-state exposure (AUC_{tau}) and change in HIV-1 RNA levels on day 11 was explored. An E_{max} model provided adequate fit to the data (see **Figure S2, Supplemental Digital Content**, <http://links.lww.com/QAI/A424>, which demonstrates the relationship between BMS-986001 AUC_{tau} on day 10 and plasma HIV-1 RNA change on day 11 from day 1, after 10 days of monotherapy with BMS-986001 from 100 to 600 mg). The relationship between BMS-986001 plasma exposure (AUC_{tau}) and change in \log_{10} plasma HIV-1 RNA levels on day 11 from day 1 was explored using nonlinear regression methods. An E_{max} model was applied to the data:

$$\begin{aligned} &\log \text{ change in plasma HIV-1 RNA } (\log_{10} \text{ copies/mL}) \\ &= E_0 + E_{max} \times AUC_{ss} / (AUC_{50} + AUC_{ss}), \end{aligned}$$

where E_0 = effect in absence of BMS-986001, E_{max} = maximum effect, AUC_{ss} = AUC at steady state, and AUC_{50} = AUC required to achieve 50% of maximum reduction in HIV-1 RNA level.

This result suggests that the BMS-986001 plasma AUC is correlated with its antiviral activity in humans. The AUC_{50} estimated from the analysis was 3485 ng·h/mL, and indicates that AUC values produced by doses from 100 to 600 mg were on the upper end of the exposure–response curve. Two non-responders ($<0.5 \log_{10}$ decline in copy number; 1 subject from the 100-mg group and 1 subject from the 600-mg group) were excluded from the analysis as although their viral load met entry criteria (>5000 copies/mL) at screening (1–21 days before initialization of treatment), by the time of randomization into the study, their viral load was <5000 copies/mL and hence did not meet entry criteria. Exclusion of these 2

TABLE 3. Summary of BMS-986001 PK Parameters

| | 100 mg | | 200 mg | |
|--|-------------------|-------------------|-------------------|-------------------|
| | Day 1 (n = 6) | Day 10 (n = 5) | Day 1 (n = 6) | Day 10 (n = 6) |
| C_{max} , geometric mean (CV), ng/mL | 1896.11 (26.78) | 1868.77 (13.80) | 3505.57 (12.62) | 3090.50 (27.05) |
| AUC_{tau} , geometric mean (CV), ng·h/mL | 6327.54 (13.61) | 6753.82 (6.59) | 12,427.84 (20.17) | 13,007.14 (32.00) |
| $CL_{T/F}$, geometric mean (CV), L/h | 15.80 (15.93) | 14.81 (6.70) | 16.09 (20.52) | 15.38 (27.58) |
| T_{max} , median (range), h | 1.0 (1.0–2.1) | 1.0 (1.0–2.0) | 1.0 (1.0–1.0) | 1.9 (1.0–2.0) |
| $T_{1/2}$, mean (SD), h | 3.61 (0.10) | 3.47 (0.51) | 4.18 (0.39) | 4.05 (0.22) |
| | 300 mg | | 600 mg | |
| | Day 1 (n = 5) | Day 10 (n = 5) | Day 1 (n = 6) | Day 10 (n = 6) |
| C_{max} , geometric mean (CV), ng/mL | 4210.56 (24.49) | 4610.44 (32.41) | 8850.43 (16.39) | 10,733.08 (24.63) |
| AUC_{tau} , geometric mean (CV), ng·h/mL | 17,105.29 (21.78) | 19,231.84 (19.94) | 39,371.00 (13.10) | 42,282.97 (14.67) |
| $CL_{T/F}$, geometric mean (CV), L/h | 17.54 (25.75) | 15.60 (21.25) | 15.24 (12.62) | 14.19 (16.46) |
| T_{max} , median (range), h | 2.0 (1.0–2.1) | 1.0 (1.0–2.2) | 2.0 (1.0–2.1) | 1.0 (0.9–2.0) |
| $T_{1/2}$, mean (SD), h | 4.00 (0.54) | 3.60 (0.68) | 3.86 (0.57) | 3.82 (0.51) |

$CL_{T/F}$, apparent total body clearance; CV, coefficient of variance; T_{max} , time to C_{max} ; $T_{1/2}$, terminal plasma half-life after the last dose administered.

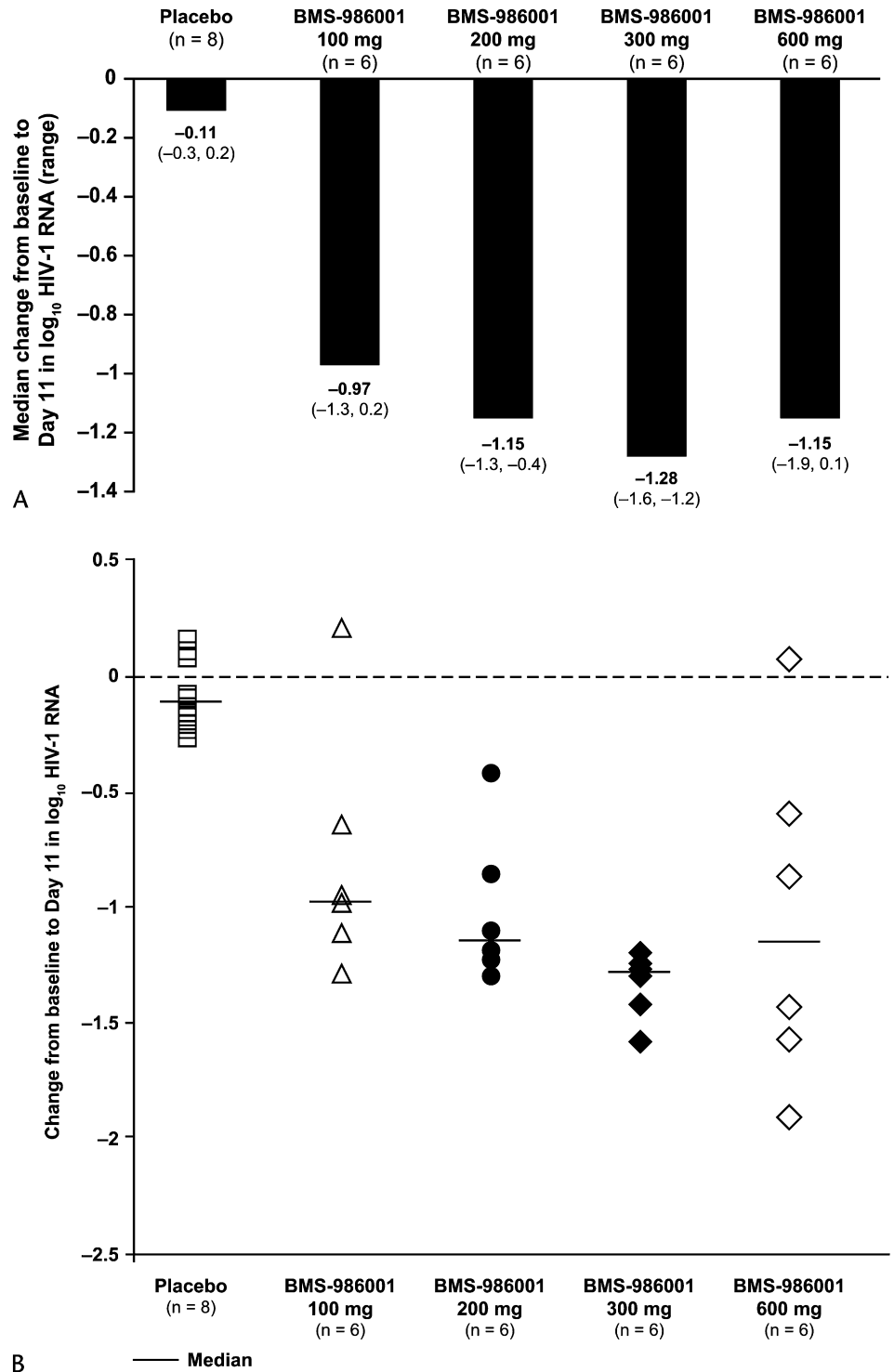


FIGURE 1. A, Median change in plasma HIV-1 RNA level from baseline. B, Individual change in plasma HIV-1 RNA level from baseline to day 11.

nonresponders improved model fitting and precision of parameter estimates.

Resistance Analysis

At baseline, only 1 subject had an NRTI resistance mutation detectable by population sequencing [see **Table S2, Supplemental Digital Content**, <http://links.lww.com/QAI/A424>, which

shows all amino acid changes from wild-type in protease and reverse transcriptase at days 1 (baseline), 11, and 17]. This subject was in the 600-mg group and had T215T/S on day 1, which was not present on days 11 or 17. Two subjects in the 300-mg group had K70K/R and K219K/R, respectively, on day 17, which were not present on days 1 or 11. All 3 subjects responded well to BMS-986001. For subjects

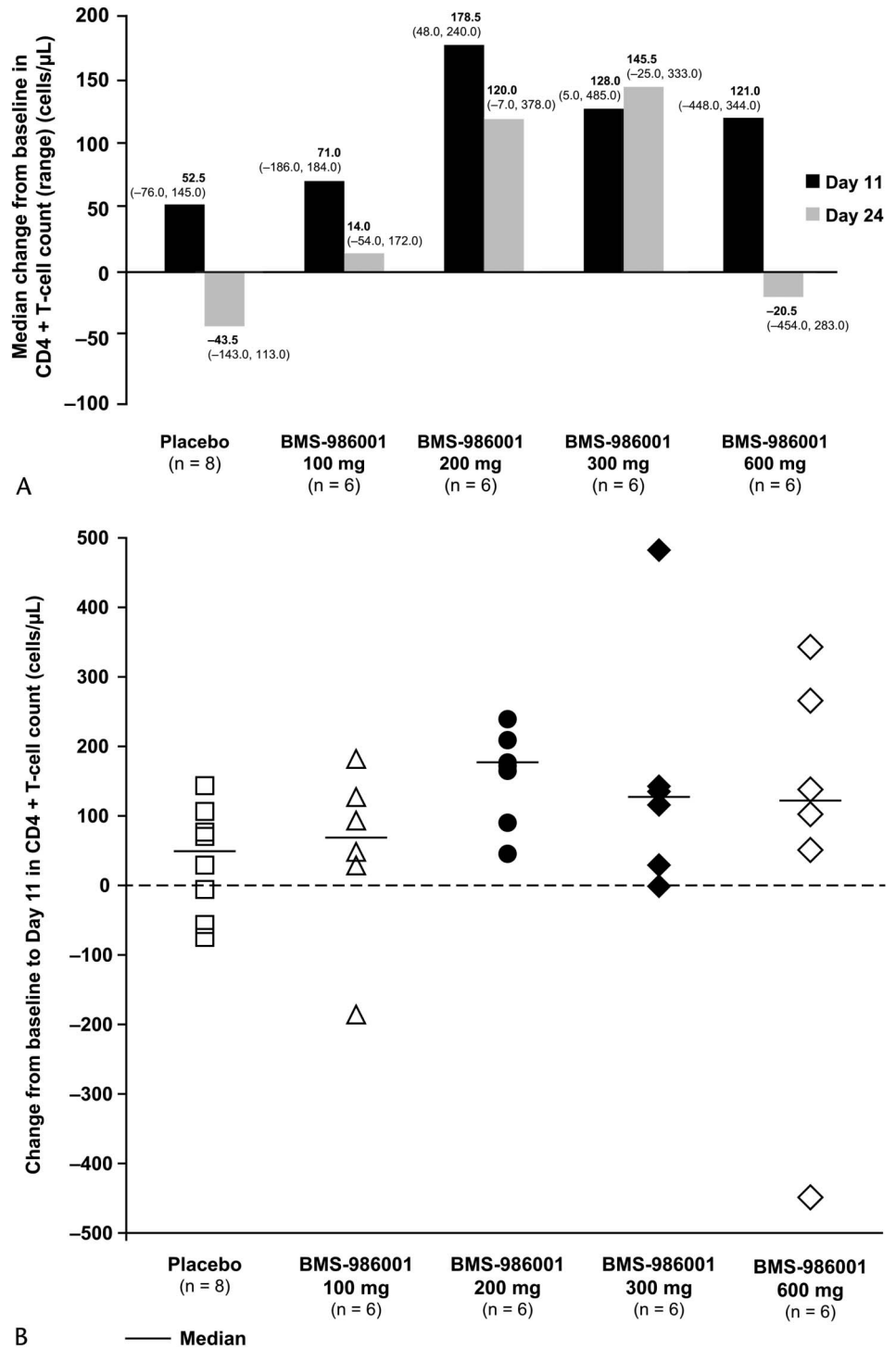


FIGURE 2. A, Median change from baseline in CD4⁺ T-cell counts. B, Individual change in CD4⁺ T-cell counts.

with the T215T/S, K70K/R, or K219K/R mutations, decline in HIV-1 RNA from baseline to day 11 was 1.91, 1.42, or 1.58 log₁₀ copies/mL, respectively. Three subjects had a decreased response to BMS-986001 (<0.5 log₁₀ decrease in HIV-1 RNA) on day 11; analysis showed that there were no NRTI-associated resistance mutations at baseline. Despite a history of previous treatment and failure to

3TC and/or FTC in several subjects, the M184V mutation was not detected at any time in any subject.

DISCUSSION

These results represent the first report of the safety and antiviral activity of the novel HIV-1 NRTI BMS-986001 in

HIV-1–infected subjects. Overall, BMS-986001 was generally well tolerated in this study. AEs did not seem to have a dose-dependent relationship and the majority were mild and deemed not related or unlikely related to study treatment. No AEs necessitated study drug discontinuation. BMS-986001 was rapidly absorbed at all doses studied, reaching C_{max} in approximately 1–2 hours. Mean plasma concentration–time profiles for BMS-986001 on days 1 and 10 were largely overlapping for all dose groups, indicating no significant accumulation in BMS-986001 systemic exposures following once daily dosing. BMS-986001 demonstrated a linear dose–exposure relationship across the dose ranges studied following 10 days of once daily dosing. The increases in plasma C_{max} and AUC were generally proportional to increases in dose. For all doses studied, BMS-986001 was rapidly absorbed and results were consistent with single-ascending-dose study results in uninfected subjects (Bristol-Myers Squibb, unpublished data, 2011).

BMS-986001 is metabolized intracellularly to its active triphosphate form. In vitro studies in CEM cells (CD4⁺ T-cell line) showed that BMS-986001 triphosphate had an intracellular $T_{1/2}$ of approximately 9.7 hours.¹⁷ The intracellular concentration of the active component over time in HIV-1–infected subjects and correlation with the extent of reduction in HIV-1 RNA is currently being evaluated.

Substantial decreases in plasma HIV-1 RNA were recorded for the majority of subjects, and the decrease at day 11 with BMS-986001 compared favorably with observations with other potent NRTIs, including TDF.¹⁸ It should be noted, however, that there are differences in the study populations between this TDF monotherapy study¹⁸ and the current study, including for example, the degree of previous exposure to antiretrovirals. A similar median decrease in plasma HIV-1 RNA of $\geq 1 \log_{10}$ was observed in all arms; therefore, antiviral activity at doses of 100–600 mg is roughly comparable. Increases from baseline in median CD4⁺ T-cell counts were also recorded in all BMS-986001 groups (except the 600-mg group) at days 11 and 24. However, high variability among individual subjects was observed within each dose group, including a fall in median CD4⁺ T-cell counts in 2 subjects. A possible contributor to the variation in CD4⁺ T-cell responses detected was the inadequate conservation of cells during transport and storage. The circadian rhythm of leukocytes and variation in complete blood cell count according to minor infections may also have contributed.

Exposure–response analysis suggested a correlation between BMS-986001 plasma AUC_{tau} and antiviral activity, with doses from 100 to 600 mg resulting in geometric mean values for plasma exposure in excess of the EC_{50} value for decline in plasma HIV-1 RNA.

Three subjects had a decreased response to BMS-986001 ($< 0.5 \log_{10}$ decrease in HIV-1 RNA) on day 11, none of whom had NRTI-associated resistance mutations at baseline or on day 11. The subjects had comparable PK to other subjects in their respective dose groups. In 1 subject, HIV-1 RNA was 15,000 copies/mL at screening, but 307 copies/mL at baseline, which contributed to the low change from baseline estimated for BMS-986001. Three other subjects who had TAMs responded well to BMS-986001. These data suggest that the decreased response in some subjects is unlikely to be due to known NRTI resistance-associated mutations.

A limitation of the study methodology, however, is that the assay used for resistance analysis did not cover the reverse transcriptase connection or RNase H domains of the HIV-1 genome. Historical genotype data were also not available. In addition, some doses were administered at home; thus, subject adherence and its impact on individual virologic response in this study cannot be determined. Variability in technical procedures may also have contributed.

In conclusion, BMS-986001 is a once daily NRTI with potent antiviral activity and linear PK. It was generally well tolerated when administered for 10 days in treatment-experienced HIV-1–infected subjects. These data support the further clinical development of BMS-986001 in cART; a phase 2b study in treatment-naive HIV-1–infected patients (NCT01489046) is ongoing. Doses of 100, 200, and 400 mg once daily are being evaluated as they are projected to produce a wide range of exposures that will allow for differentiation of safety and efficacy and provide critical data for the optimal selection of a phase 3 dose.

ACKNOWLEDGMENTS

MedDRA is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations. The study design and conduct was funded by Oncology Pharma; data analysis was funded by Bristol-Myers Squibb. Editorial assistance during manuscript development was provided by Clemence Hindley and Roseanne Girnary of MediTech Media and was funded by Bristol-Myers Squibb.

REFERENCES

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1–infected Adults and Adolescents: 2012 Update. Washington, DC: U.S. Department of Health and Human Services; 2012. Available at: <http://aidsinfo.nih.gov/contentfiles/lv-guidelines/adultandadolescentgl.pdf>. Accessed June 1, 2013.
2. European AIDS Clinical Society. Guidelines Version 6. Paris, France: EACS; October 2011. Available at: <http://www.europeanaidscinicalsociety.org/images/stories/EACS-Pdf/EACSGuidelines-v6.0-English.pdf>. Accessed June 1, 2013.
3. World Health Organization. *Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach 2010 Revision*. 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf. Accessed June 1, 2013.
4. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther*. 2001;23:1603–1614.
5. Islam FM, Wu J, Jansson J, et al. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med*. 2012;13:453–468.
6. Patel P, Bush T, Overton T, et al. Effect of abacavir on acute changes in biomarkers associated with cardiovascular dysfunction. *Antivir Ther*. 2012;17:755–761.
7. Bedimo R, Maalouf NM, Zhang S, et al. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS*. 2012;26:825–831.
8. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS*. 2012;26:867–875.
9. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372:293–299.
10. Dutschman GE, Grill SP, Gullen EA, et al. Novel 4'-substituted stavudine analog with improved anti-human immunodeficiency virus activity and decreased cytotoxicity. *Antimicrob Agents Chemother*. 2004;48:1640–1646.

11. Yang G, Dutschman GE, Wang CJ, et al. Highly selective action of triphosphate metabolite of 4'-ethynyl D4T: a novel anti-HIV compound against HIV-1 RT. *Antiviral Res.* 2007;73:185–191.
12. Yang G, Painsil E, Dutschman GE, et al. Impact of novel human immunodeficiency virus type 1 reverse transcriptase mutations P119S and T165A on 4'-ethynylthymidine analog resistance profile. *Antimicrob Agents Chemother.* 2009;53:4640–4646.
13. Li Z, Terry B, Olds W, et al. The in vitro cross-resistance profile of the NRTI BMS-986001 against known NRTI resistance mutations. Presented at: International Workshop on HIV & Hepatitis Virus Drug Resistance; June 5-9, 2012; Spain.
14. Clumeck N, Pozniak A, Raffi F. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults. *HIV Med.* 2008;9:65–71.
15. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31–41.
16. Gough K, Hutchison M, Keene O, et al. Assessment of dose proportionality: report from the Statisticians in the Pharmaceutical Industry/ Pharmacokinetics UK Joint Working Party. *Drug Inf J.* 1995;29:1039–1048.
17. Wang X, Tanaka H, Baba M, et al. Retention of metabolites of 2',3'-didehydro-3'-deoxy-4'-ethynylthymidine, a novel anti-human immunodeficiency virus type 1 thymidine analog, in cells. *Antimicrob Agents Chemother.* 2009;53:3317–3324.
18. Barditch-Crovo P, Deeks SG, Collier A, et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother.* 2001;45:2733–2739.