# Efficacy, safety, bone and metabolic effects of HIV nucleoside reverse transcriptase inhibitor BMS-986001 (AI467003): a phase 2b randomised, controlled, partly blinded trial

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## Summary

**Background** BMS-986001 is a thymidine analogue nucleoside reverse transcriptase inhibitor (NRTI) designed to maintain in-vitro antiviral activity while minimising off-target effects. We assessed the efficacy and safety of BMS-986001 versus tenofovir disoproxil fumarate in treatment-naive patients with HIV-1.

**Methods** In this phase 2b, randomised, active-controlled trial (AI467003), we recruited treatment-naive (no current or previous exposure to an antiretroviral drug for >1 week) adults (aged at least 18 years) with HIV-1 from 47 sites across Asia, Australia, Europe, North America, South Africa, and South America. Patients with plasma HIV-1 RNA greater than 5000 copies per mL and CD4 counts greater than 200 cells per μL were randomly assigned (2:2:2:3) to receive BMS-986001 100 mg, 200 mg, or 400 mg once a day or to receive tenofovir disoproxil fumarate 300 mg once a day; each allocation was given with efavirenz 600 mg once a day and lamivudine 300 mg once a day. Both patients and investigators were masked to BMS-986001 dose (achieved with similar looking placebo tablets), but not allocation up to and including week 48. The primary endpoints were the proportion of patients with plasma HIV-1 RNA less than 50 copies per mL and safety events (serious adverse events and adverse events leading to discontinuation) through week 24; the main analysis was with a modified intention-to-treat population. Resistance analysis was a secondary endpoint, and additional safety parameters were exploratory endpoints. This trial is registered with ClinicalTrials.gov, number NCT01489046, and the European Clinical Trials Database, number EudraCT 2011-003329-89.

**Findings** Patients were recruited between Jan 25, 2012, and Oct 3, 2012; 757 patients were assessed for eligibility and 301 were randomly assigned to receive either BMS-986001 once a day (67 patients to 100 mg, 67 to 200 mg, and 66 to 400 mg) or tenofovir disoproxil fumarate (n=101). 297 patients received at least one dose of study drug. At week 24, 57 (88%) of 65 patients for whom there were data in the 100 mg group, 54 (81%) of 67 in the 200 mg group, 62 (94%) of 66 in the 400 mg group achieved HIV-1 RNA less than 50 copies per mL, compared with 88 (89%) of 99 in the tenofovir disoproxil fumarate group (modified intention-to-treat population). BMS-986001 was generally well tolerated through week 48. Two patients had BMS-986001-related serious adverse events (atypical drug eruption and thrombocytopenia) and two in the tenofovir disoproxil fumarate group had study drug-related serious adverse events (potential drug-induced liver injury and depression or lipodystrophy) that led to discontinuation. NRTI resistance-associated mutations were reported in four (2%) of 198 patients, and non-NRTI mutations in 17 (9%) of 198 patients receiving BMS-986001 versus none of 99 and one (1%) of 99 patients receiving tenofovir disoproxil fumarate, respectively. Compared with tenofovir disoproxil fumarate, individuals in the BMS-986001 groups showed a smaller decrease in lumbar spine and hip bone mineral density but greater accumulation of limb and trunk fat, subcutaneous and visceral adipose tissue, and increased total cholesterol.

**Interpretation** BMS-986001 had similar efficacy to that of tenofovir disoproxil fumarate and was associated with a smaller decrease in bone mineral density; however, greater resistance and gains in both peripheral and central fat accumulation were recorded for the investigational drug. Bristol-Myers Squibb has discontinued its involvement in the development of BMS-986001, and future decisions on development will be made by Oncolys BioPharma.

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## Introduction

Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) are the backbone agents upon which most combination antiretroviral therapy (ART) for HIV is built. Treatment guidelines recommend that regimens for treatment-naive patients incorporate two NRTIs and one other class of agent, such as an integrase inhibitor or a protease inhibitor with a pharmacokinetic enhancer (eg, cobicistat or ritonavir).[1,2]

Despite the widespread use of NRTIs in first-line treatment regimens, they are associated with toxic effects, which can lead to long-term complications. These can include decreased bone mineral density,[3] lipoatrophy,[4,5] anaemia, pancreatitis,[6,7] and hypersensitivity reaction.[8] Several NRTIs, including didanosine, stavudine, and zidovudine, are not used routinely because of toxic effects associated with mitochondrial dysfunction, namely peripheral neuropathy,[9,10] lipoatrophy,[4,5] hepatic steatosis,[11]

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and metabolic acidosis.[12,13] Thus, there is a need for NRTIs with potent anti-HIV-1 activity, tolerability profiles better than available drugs, long-term safety that is favourable in terms of bone mineral density and renal function, and limited cross-resistance to existing drugs of this class.

BMS-986001 (also known as OBP-60) is a thymidine analogue NRTI (an analogue of stavudine) specifically designed to maintain the in-vitro antiviral activity shown by other NRTIs and minimise off-target effects that cause toxic effects.[14,15] Findings of in-vitro experiments have shown that BMS-986001 has potent antiviral activity and reduced mitochondrial toxicity compared with that of stavudine.[15,16] BMS-986001 also has reduced inhibition of host DNA polymerases[14,15] and, in preclinical studies, was not associated with bone or renal toxic effects.[17] Furthermore, BMS-986001 has activity against most HIV-1 subtypes (Bristol-Myers Squibb, unpublished data, 2011) and against HIV-1 isolates with certain NRTI resistance-associated

mutations, including Lys65Arg, Leu74Val, and the Gln151Met constellation (without Met184Val).[18] Met184Val induced a low-level decrease (2 to 3 fold) in viral susceptibility to BMS-986001.[18]

In a phase 2a, dose-escalating, monotherapy study[19] in treatment-experienced patients with HIV-1 who were not exposed to any antiretroviral treatment in the 3 months before study start, BMS-986001 given for 10 days showed a median decrease in HIV-1 RNA from baseline of at least 1 $\log_{10}$ copies per mL for all doses. These findings were used to support the design of this dose-finding phase 2b study, which aimed to assess the efficacy and safety of three doses of BMS-986001 (100 mg, 200 mg, and 400 mg once a day) versus tenofovir disoproxil fumarate (300 mg once a day), when given with efavirenz (600 mg once a day) and lamivudine (300 mg once a day) in treatment-naive patients with HIV-1. We did a detailed assessment of bone, renal, metabolic, and mitochondrial parameters to assess the safety of BMS-986001.

## Methods

### Study design

AI467003 was a phase 2b, randomised, active-controlled, blinded-to-BMS-986001 dose trial done at 47 sites across Asia, Australia, Europe, North America, South Africa, and South America. This study was done in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study was done in compliance with the protocol. The protocol and any amendments and the participant informed consent received institutional review board or independent ethics committee approval or favourable opinion before initiation of the study.

### Patients

Eligible patients were treatment-naive (defined as no current or previous exposure to an antiretroviral drug for more than 1 week), HIV-1-infected adults aged at least 18 years with plasma HIV-1 RNA greater than 5000 copies per mL and CD4 counts greater than 200 cells per µL at screening. Exclusion criteria included a history of phenotypic or genotypic drug resistance testing showing resistance to efavirenz, tenofovir disoproxil fumarate, or lamivudine, presence of hepatitis B surface antigen, hepatitis C virus antibody or RNA, history of abnormal liver transaminases (defined as greater than three times the upper limit of normal) at screening, and creatinine clearance less than 60 mL/min at screening. All patients provided written informed consent in agreement with the principles of the Declaration of Helsinki.

### Randomisation and masking

Eligible patients were randomly assigned (2:2:2:3) into four treatment groups: one of three doses of BMS-986001 (100, 200 or 400 mg once a day) and a reference group of tenofovir disoproxil fumarate (300 mg once a day), each with a common background treatment of efavirenz (600 mg once a day) and lamivudine (300 mg once
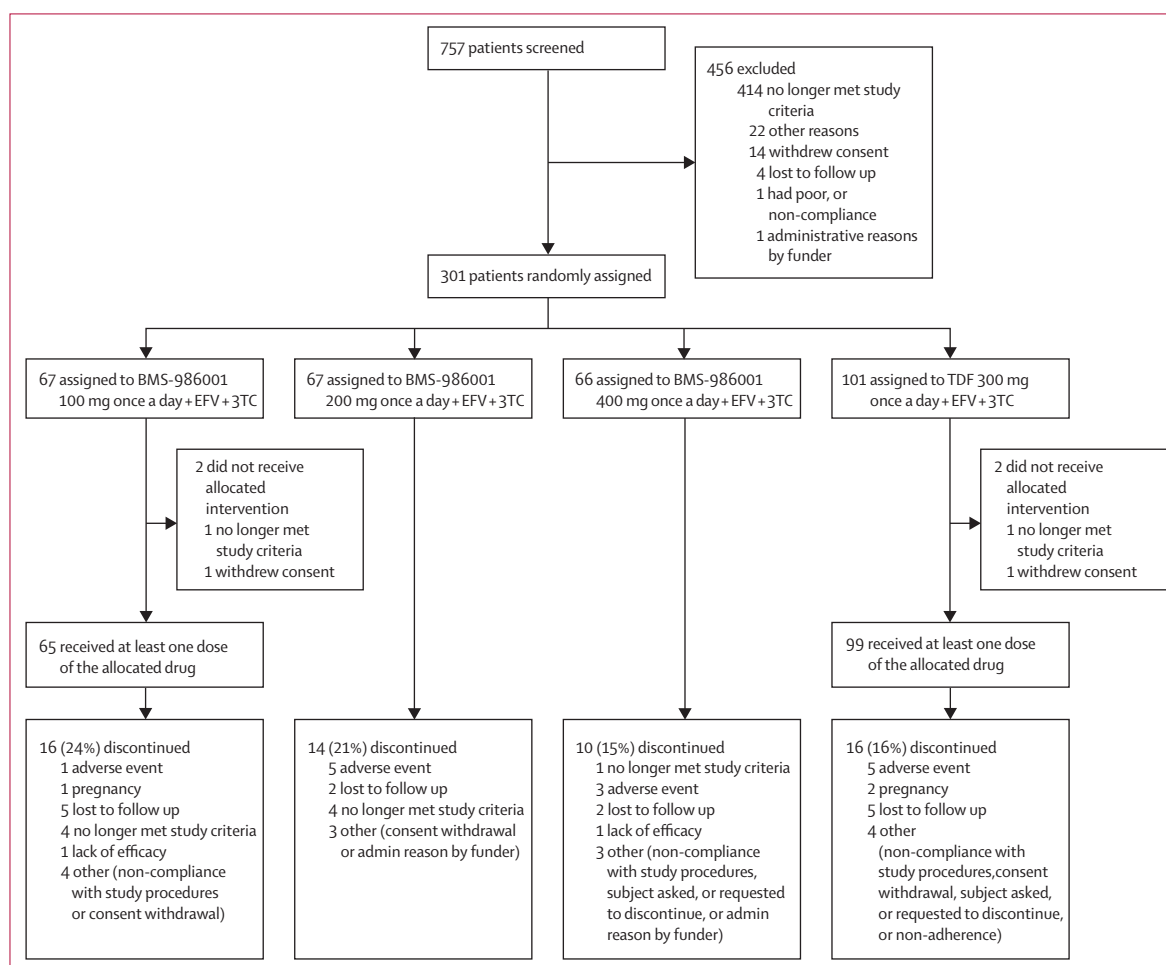


*Figure 1:* Trial profile
3TC=lamivudine. EFV=efavirenz. TDF=tenofovir disoproxil fumarate.

a day). Efavirenz and lamivudine were selected for their known safety profiles, which allowed for reasonable assessment of the specific safety profile of BMS-986001 when used as a component of ART, and also their common use worldwide as first-line treatments.

For patients who met the protocol eligibility criteria, randomisation was done with a computer-generated code and stratified according to baseline viral load (HIV-1 RNA <100 000 copies per mL *vs* HIV-1 RNA at least 100 000 copies per mL). Both patients and investigators were masked to BMS-986001 dose, but not allocation, up to and including week 48. BMS-986001 dose masking was done with once a day dosing for all BMS-986001 treatment groups and similar looking placebo tablets. Funders were unblinded to BMS-986001 doses after the last patient had reached week 24 and patients and investigators were unblinded after the last patient had reached week 48.

| | BMS-986001 | | | Tenofovir disoproxil fumarate, 300 mg once a day (N=99) |
|---|---|---|---|---|
| | 100 mg once a day (N=65) | 200 mg once a day (N=67) | 400 mg once a day (N=66) | |
| Age (years) | 31 (18–64) | 32 (18–53) | 34 (19–57) | 29 (18–61) |
| **Sex** | | | | |
| Men | 43 (66%) | 42 (63%) | 41 (62%) | 70 (71%) |
| Women | 22 (34%) | 25 (37%) | 25 (38%) | 29 (29%) |
| **Race** | | | | |
| Black | 31 (48%) | 32 (48%) | 35 (53%) | 40 (40%) |
| Asian | 15 (23%) | 15 (22%) | 14 (21%) | 27 (27%) |
| White | 11 (17%) | 10 (15%) | 7 (11%) | 15 (15%) |
| Other* | 8 (12%) | 10 (15%) | 10 (15%) | 17 (17%) |
| Median baseline BMI (kg/m²; IQR) | 23·9 (21·2–28·4) | 23·8 (21·5–26·8) | 22·3 (19·9–26·3) | 23·3 (20·5–29·0) |
| **Baseline adipose tissue (cm²)** | | | | |
| Median subcutaneous adipose tissue (IQR) | 110·7 (43·8–184·5) | 89·6 (61·6–141·3) | 68·1 (37·9–154·4) | 71·0 (43·7–156·7) |
| Median total adipose tissue (IQR) | 181·0 (79·0–266·2) | 141·9 (74·8–211·4) | 100·3 (60·2–208·6) | 107·5 (74·6–266·2) |
| Median visceral adipose tissue (IQR) | 37·4 (21·4–73·7) | 33·4 (12·9–68·4) | 32·2 (15·7–54·0) | 33·2 (15·8–69·2) |
| **HIV-1 subtype** | | | | |
| AE | 14 (22%) | 13 (19%) | 8 (12%) | 25 (25%) |
| B | 28 (43%) | 22 (33%) | 24 (36%) | 36 (36%) |
| C | 22 (34%) | 30 (45%) | 29 (44%) | 33 (33%) |
| Other | 1 (2%) | 2 (3%) | 5 (8%) | 5 (5%) |
| Median baseline viral load (HIV-1 RNA), log₁₀ copies per mL (IQR) | 4·34 (4·0–4·8) | 4·43 (4·0–4·8) | 4·46 (4·0–4·8) | 4·38 (4·0–4·8) |
| Proportion of patients with ≥100 000 copies per mL | 11 (17%) | 12 (18%) | 12 (18%) | 17 (17%) |
| Median baseline CD4 count, cells per µL (IQR) | 290 (252–384) | 325 (254–406) | 330 (253–410) | 330 (253–410) |
| Patients with <200 cells per µL | 6 (9%) | 3 (5%) | 4 (6%) | 12 (12%) |

Data are median (range), n (%), or median unless otherwise stated. Study drugs given as combination antiretroviral therapy with efavirenz plus lamivudine. *Most patients within the other category reported themselves as multiracial.

*Table 1:* Baseline demographic and disease characteristics

## Procedures

Study visits were completed at screening and weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48 (or upon early termination) during the study. Plasma HIV-1 RNA concentrations were quantified by PCR with the Abbott m2000 RealTime System (Abbott Molecular, Des Plaines, IL, USA). Protocol-defined virological failure was defined as confirmed plasma HIV-1 RNA at least 50 copies per mL at week 24, or later (confirmed by second measurement within 4 weeks of the original sample), or virological rebound (confirmed HIV-1 RNA at least 50 copies per mL at any time after already confirmed suppression to less than 50 copies per mL, or confirmed increase in HIV-1 RNA greater than 1 log₁₀ copies per mL above nadir at any time [where nadir is at least 50 copies per mL]).

We tested for viral drug resistance at screening and in the event of confirmed protocol-defined virological failure, or at a minimum in the event of a confirmed plasma HIV-1 RNA measurement of at least 400 copies per mL at any time during the study (having previously achieved viral suppression of less than 50 copies per mL) or discontinuation before achieving viral suppression after week 8 with a last plasma HIV-1 RNA measurement of at least 400 copies per mL. Genotypic and phenotypic resistance testing were done with the GenoSure MG (screening) and the Phenosense GT (failure) assays (both Monogram Biosciences, San Francisco, CA, USA).

Physical examinations, measurement of vital signs, and clinical laboratory assessments were done at selected times throughout the study, and patients were closely monitored for adverse events and serious adverse events throughout. Adverse events were coded according to MedDRA (version 16.0) and the severity and association with study drug was assessed by the corresponding local investigator. Dual-energy x-ray absorptiometry (DXA) scans for measurement of bone mineral density (hip and lumbar spine) and limb or trunk fat (whole body DXA scans) were done at baseline and weeks 24 and 48, or upon early termination. Single slice CT scans of the abdomen for measurement of visceral adipose tissue, subcutaneous adipose tissue, and total adipose tissue were done at baseline and week 48, or upon early termination. For both DXA and CT scans, standardisation and masked central reading were done by BioClinica (Newtown, PA, USA). Subcutaneous fat was obtained from a 3 mm skin punch biopsy from the lower abdomen or buttock area, from consenting patients, for measurement of mitochondrial DNA (mtDNA) content at baseline and weeks 24 and 48, or upon early termination. The fat samples were separated from the overlying skin and stored in RNAlater at –70°C freezer until batch processing at the end of the study. Quantification of mtDNA content was done as described previously[20] with an optimised DNA input of 1 µg per 20 µL reaction. We assessed laboratory measurements, including CD4

cell counts, and serum creatinine for estimation of creatinine clearance.

## Outcomes

Primary endpoints were proportion of patients with plasma HIV-1 RNA less than 50 copies per mL at week 24 and the frequency of serious adverse events and adverse events leading to discontinuation through week 24. Secondary endpoints were proportion of patients with plasma HIV-1 RNA less than 50 copies per mL at week 48 and the frequency of serious adverse events and adverse events leading to discontinuation through week 48. Additional secondary endpoints were change from baseline in CD4 cell counts and the number of patients with virological failure who had virus exhibiting genotypic drug resistance-associated mutations through weeks 24 and 48.

Exploratory endpoints were assessment of the effect of BMS-986001 and tenofovir disoproxil fumarate on change from baseline in mtDNA copy number, bone mineral density, body fat distribution, fasting lipid profile, and renal function at weeks 24 and 48.

## Statistical analysis

This study was designed to estimate the effects of the randomly assigned study drug. Thus, sample size considerations were based on the precision with which these effects can be estimated and not on the ability of the study to find significant differences between treatment groups. Assuming a response rate of 80%, a target sample size of roughly 300 randomly assigned patients (67 per BMS-986001 dose group and 100 in the tenofovir disoproxil fumarate dose group) would provide a 95% exact binomial CI that extends from 69% to 89% for a BMS-986001 group (n=67) or from 71% to 87% for the tenofovir disoproxil fumarate group (n=100).

The primary efficacy endpoint assessment used the US Food and Drug Administration defined snapshot algorithm that takes the last plasma HIV-1 RNA in the predefined week 24 and 48 visit windows (+/− 6 weeks) to establish response. Thus, the modified intention-to-treat population consisted of patients who received at least one dose of BMS-986001 or tenofovir disoproxil fumarate. An observed-population analysis used data for patients who received at least one dose of BMS-986001 or tenofovir disoproxil fumarate, with plasma HIV-1 RNA measurements within the week 24 and 48 periods.

The percentage change from baseline in hip bone mineral density was analysed with an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and baseline value as a covariate. The analyses were done with the data restricted to baseline and the time of interest (week 24 or week 48). This method was intended to increase the precision of the estimates by removing variability attributable to baseline differences.

The trial is registered with ClinicalTrials.gov, number NCT01489046, and the European Clinical Trials Database, number EudraCT 2011-003329-89.

## Role of the funding source

Individuals employed by the funder participated in the study design, data collection, data analysis, and data interpretation, in conjunction with external study investigators. The first draft of the manuscript was prepared by a professional medical writer, paid for by the sponsor, and edited and revised by all authors. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between Jan 25, 2012, and Oct 3, 2012, patients were enrolled from 47 sites. 757 patients were screened, of which 301 were randomly assigned and 297 received treatment (figure 1). Most screening failures were due to failure to meet entry criteria; the most common reasons were a screening plasma HIV-1 RNA less than 5000 copies per mL (238/456 [52%]) and CD4 count less than 200 cells per µL (79/456 [17%]). Of those receiving treatment, 40 (20%) of 198 patients in the BMS-986001 groups and 16 (16%) of 99 in the tenofovir disoproxil fumarate group, had discontinued from the study by the week 48 database lock (figure 1).

| | BMS-986001 | | | Tenofovir disoproxil fumarate, 300 mg once a day (N=99) |
|---|---|---|---|---|
| | 100 mg once a day (N=65) | 200 mg once a day (N=67) | 400 mg once a day (N=66) | |
| **mITT analysis (FDA snapshot algorithm) at week 24** | | | | |
| HIV-1 RNA <50 copies per mL | 57 (88%) | 54 (81%) | 62 (94%) | 88 (89%) |
| HIV-1 RNA ≥50 copies per mL* | 8 (12%) | 9 (13%) | 4 (6%) | 7 (7%) |
| No virological data at week 24 | | | | |
| Discontinued due to adverse event or death | 0 | 4 (6%) | 0 | 2 (2%) |
| Discontinued for other reason | 0 | 0 | 0 | 2 (2%) |
| Missing data during window but on-study | 0 | 0 | 0 | 0 |
| **mITT analysis (FDA snapshot algorithm) at week 48** | | | | |
| HIV-1 RNA <50 copies per mL | 49 (75%) | 54 (81%) | 59 (89%) | 81 (82%) |
| HIV-1 RNA ≥50 copies per mL* | 12 (19%) | 8 (12%) | 3 (5%) | 8 (8%) |
| No virological data at week 48 | | | | |
| Discontinued due to adverse event or death | 0 | 5 (7%) | 2 (3%) | 4 (4%) |
| Discontinued for other reason | 4 (6%) | 0 | 1 (1·5%) | 6 (6%) |
| Missing data during window but on-study | 0 | 0 | 1 (1·5%) | 0 |
| **Observed analysis at week 24** | | | | |
| Observed population | 62 | 57 | 64 | 91 |
| HIV-1 RNA <50 copies per mL | 57 (92%) | 54 (95%) | 62 (97%) | 88 (97%) |
| **Observed analysis at week 48** | | | | |
| Observed population | 51 | 54 | 59 | 84 |
| HIV-1 RNA <50 copies per mL | 49 (96%) | 54 (100%) | 59 (100%) | 81 (96%) |

Data are n or n (%). Study drugs given as combination antiretroviral therapy with efavirenz plus lamivudine. mITT=modified intention to treat. TDF=tenofovir disoproxil fumarate. *Virological failure.

*Table 2:* Proportion of patients with plasma HIV-1 RNA <50 copies per mL at weeks 24 and 48

Baseline demographic and disease characteristics were similar in all treatment groups (table 1); the median age of patients was 31 years, two-thirds of patients were men, and almost half were black or African–American. Most patients had HIV-1 subtypes C (38%), B (37%), or AE (20%). Median baseline HIV-1 RNA 4·39 log$_{10}$ copies per mL (18% had at least 100 000 copies per mL) and median baseline CD4 count was 307·0 cells per µL (8% had fewer than 200 cells per µL).

At week 24, 81–94% of patients in the BMS-986001 treatment groups and 89% in the tenofovir disoproxil fumarate treatment group had achieved HIV-1 RNA less than 50 copies per mL (table 2). By week 48, 75–89% of patients receiving BMS-986001 and 82% receiving tenofovir disoproxil fumarate had HIV-1 RNA less than 50 copies per mL. At week 24, in the BMS-985001 treatment groups, CD4 counts increased from baseline by a median of 157·0 cells per µL (IQR 104·0–236·0) in the 100 mg group, 127·0 cells per µL (67·0–192·0) in the 200 mg group, and 139·0 cells per µL (49·0–199·0) in the 400 mg groups; in the tenofovir disoproxil fumarate group, median increase was and 119·0 cells per µL (IQR 54·0–188·0). By week 48 median increases were 171·0 cells per µL (IQR 74·0–286·0), 139·5 cells per µL (IQR 69·0–248·5), and 155·0 cells per µL (IQR 97·0–225·0) BMS-986001 groups, and 147·5 cells per µL (IQR 79·0–281·0) for tenofovir disoproxil fumarate.

Through the week 48 database lock, 18 (9%) of 198 patients in the BMS-986001 groups and four (4%) of 99 patients in the tenofovir disoproxil fumarate group met on-study criteria for resistance testing. Of these,

16 (89%) of 18 patients in the BMS-986001 group and one (25%) in four in the tenofovir disoproxil fumarate group were successfully tested. Data from five additional patients were received shortly after the week 48 database lock (table 3). We combined both datasets and noted that four (2%) of 198 patients in the BMS-986001 groups and none of the 99 patients in the tenofovir disoproxil fumarate group had developed NRTI resistance-associated mutations, and Met184Val was the only NRTI resistance-associated mutation recorded (2%). Additionally, 17 (9%) of 198 patients in the BMS-986001 groups and one (1%) of 99 in the tenofovir disoproxil fumarate group developed non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated mutations with Lys103Asn the most common (7%; table 3). Overall, the BMS-986001 100 mg group had the most NNRTI and NRTI resistance-associated mutations.

BMS-986001 was generally well tolerated through week 48. Some grade 2–4-related adverse events were more common in patients taking BMS-986001 than in those taking tenofovir disoproxil fumarate (appendix p 3), these included skin and subcutaneous tissue disorders (6·1–12·3% vs 4%), metabolic disorders (mainly high cholesterol; 1·5–7·6% vs 1·0%), and gastrointestinal disorders (1·5–6·2% vs 1·0%). Serious adverse events were reported in 19 (10%) of 198 patients across the BMS-986001 groups and in nine (9%) of 99 in the tenofovir disoproxil fumarate group (appendix p 4). Two patients had BMS-986001-related serious adverse events: atypical drug eruption and thrombocytopenia. A woman aged 49 years developed genital ulcers and episcleritis 7 days after starting treatment and oral ulcers 5 days later, leading to admittance to hospital. Ulcer swabs were PCR-negative for cytomegalovirus and herpes simplex virus. The woman received aciclovir, xylocaine–epinephrine, and dexamethasone, and the serious adverse event resolved. A man aged 25 years developed an asymptomatic decrease in platelet count (without other haematological dyscrasias), which started 3 months after and progressed during 1 year of treatment. The serious adverse event resolved without intervention after treatment completion. Two patients in the tenofovir disoproxil fumarate group also had study drug-related serious adverse events (potential drug-induced liver injury and depression or lipodystrophy) that led to discontinuation. One non-study-related death occurred (pneumonia) in the BMS-986001 200 mg once a day group. Grade 2–4 laboratory abnormalities were transient and mostly did not lead to discontinuation.

Average change from baseline in lumbar spine bone mineral density (calculated with baseline-adjusted ANCOVA [data not shown]) for BMS-986001 was –0·9% (95% CI –1·3 to –0·5) at week 24 and –1·4% (–1·9 to –0·8) at week 48, compared with –3·0% (–3·6 to –2·4) and –3·2% (–4·1 to –2·4) for tenofovir disoproxil fumarate (figure 2A). Similarly, average change from baseline in hip bone mineral density for

| | BMS-986001 | | | Tenofovir disoproxil fumarate, 300 mg once a day (N=99) |
|---|---|---|---|---|
| | 100 mg once a day (N=65) | 200 mg once a day (N=67) | 400 mg once a day (N=66) | |
| Met criteria for resistance testing* | 10 | 6 | 2 | 4 |
| Genotype determinable* | 10 | 4 | 2 | 1 |
| NNRTI resistance-associated mutations | 9 (14%) | 4 (6%) | 4 (6%)† | 1 (1%)‡ |
| Lys103Asn | 8 | 3 | 3 | 1 |
| Val106Met | 1 | 1 | 0 | 0 |
| Tyr188Cys | 1 | 0 | 0 | 0 |
| Gly190Ala | 1 | 0 | 1 | 0 |
| NRTI resistance-associated mutation | 3 (5%) | 0 | 1 (2%) | 0 |
| Met184Val | 3 | 0 | 1 | 0 |

Data are n or n (%). Study drugs given as combination antiretroviral therapy with efavirenz plus lamivudine. NNRTI=non-nucleoside reverse-transcriptase inhibitor. NRTI=nucleoside reverse-transcriptase inhibitor. *Minimum criteria for resistance testing: confirmed HIV-1 RNA >400 copies per mL after achieving viral suppression (HIV-1 RNA <50 copies per mL); or discontinuation from study treatment before achieving viral suppression after week 8, with last plasma HIV-1 RNA >400 copies per mL; all data available up to the week 48 database lock. †Two patients developed efavirenz resistance-associated mutation (week 40 and week 12) and provided data after database lock. ‡One patient developed efavirenz resistance-associated mutation (week 32) and provided data after database lock. Additionally, one patient in the 100 mg (week 56) and one patient in the 400 mg (week 56) groups developed efavirenz resistance-associated mutation and provided data after database lock.

*Table 3:* Treatment-emergent resistance or reduced susceptibility to study drugs

BMS-986001 was −0·5% (−0·8 to −0·2) at week 24 and −1·2% (−1·6 to −0·75) at week 48, compared with −1·7% (CI −2·2 to −1·2) and −3·0% (−3·7 to −2·4) for tenofovir disoproxil fumarate (figure 2B). Concordant with the smaller decreases in bone mineral density for BMS-986001, the percentage changes from baseline for biomarkers of bone resorption, C-terminal telopeptide of type I collagen, and bone formation, serum type 1 procollagen N-terminal, bone sialoprotein, osteocalcin, were lower in the BMS-986001 groups than in the tenofovir disoproxil fumarate group (appendix p 1). Mean change in creatinine clearance at week 48 was 4·0 (standard error [SE] 3·0) for the BMS-986001 100 mg group, 1·1 (1·8) for the 200 mg group, −1·6 (2·7) mL/min for the 400 mg group, and 0·048 (1·9) mL/min for the tenofovir disoproxil fumarate group.

DXA measurements showed that mean percentage increase in limb fat at week 24 in the BMS-986001 100 mg group was 4·5% (SE 2·9), 2·3% (1·8) in the 200 mg group, and 10·0% (3·0) in the 400 mg group, compared with 1·2% (1·7) increase for patients given tenofovir disoproxil fumarate. At week 48 the increases in limb fat were greater in the BMS-986001 groups than in the tenfovir group: 12·0% (5·0), 8·0% (2·9), and 15·8% (4·7) compared with 2·1% (1·9). Trunk fat increased at week 24 across the BMS-986001 groups by a mean percentage of 2·3% (2·9) in the 100 mg group, 1·3% (1·6) in the 200 mg group, and 12·7% (4·1) in the 400 mg group, and by 2·5% (2·5) in the tenofovir disoproxil fumarate group. At week 48, the BMS-986001 groups reported increases in trunk fat of 8·3% (3·6) in the 100 mg group, 7·0% (2·6) in the 200 mg group and 18·4% (6·2) in the 400 mg group, compared with the lower 3·8% (3·1) for tenofovir disoproxil fumarate.

In the BMS-986001 groups, loss in baseline limb fat of at least 10% at week 24 was reported in six (11%) of 53 patients in the 100 mg group (95% CI 4–23), seven (15%) of 47 patients in the 200 mg group (6–28), and six (11%) of 53 (4–23) patients in the 400 mg, compared with 13 (19%) of 69 (10–30) patients in the tenofovir disoproxil fumarate group. At week 48, this outcome was reported in four (9%) of 45 patient in the 100 mg group (2–21), six (13%) of 45 in the 200 mg group (5–26), and six (12%) of 51 in the 400 mg group (4–24), compared with the slightly higher 13 (20%) of 65 patients in the tenofovir disoproxil fumarate group (11–32). Loss in baseline limb fat of at least 20% at week 24 was reported in four (8%) of 53 (2–18]) in the BMS-986001 100 mg group, one (2%) of 47 ( 0–11) in the 200 mg group, two (3·8%) of 53 (1–13) in the 400 mg group, which did not differ significantly from four (6%) of 69 (2–14) patients receiving tenofovir disoproxil fumarate. At week 48, this was reported in three (7%) of 45 (1–18), two (4%) of 45 (1–15), four of (8%) of 51 (2–19) in the BMS-986001 groups and five (8%) of 65 (2–17) patients receiving tenofovir disoproxil fumarate.

CT scans showed greater gains in mean percentage subcutaneous adipose tissue and visceral adipose tissue
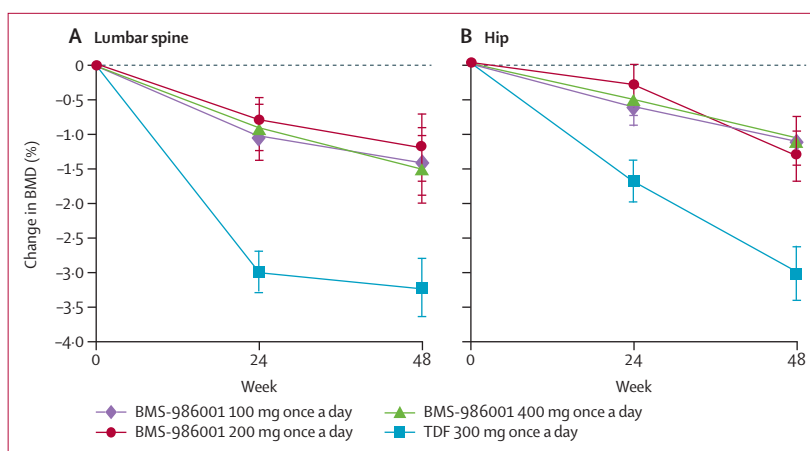


*Figure 2:* **Mean percent change in BMD by DXA**
(A) Lumbar spine and (B) Hip, from baseline to week 24 and 48. BMD=bone mineral density. SE=standard error of the mean. Error bars are standard error.

across the BMS-986001 groups compared with the tenofovir disoproxil fumarate group (appendix p 2). The greatest changes from baseline in subcutaneous adipose tissue and visceral adipose tissue occurred in the BMS-986001 400 mg group. Mean change in mtDNA copy number (extracted from subcutaneous fat biopsies) at week 48 was 3·9% (SE 5·9, n=47) in the BMS-986001 100 mg group, −1·0% (SE 6·8] n=50) in the 200 mg group, and −3·7% (SE 6·4, n=55) in the 400 mg group, and −2·5% (SE 5·6, n=72) in the tenofovir disoproxil fumarate group. We recorded a numerically greater increase in total cholesterol across the BMS-986001 groups at week 24 (mean change from baseline in total cholesterol 23·3 mg/dL [SE 3·5] in the 100 mg group, 34·3 mg/dL [3·5] in the 200 mg group, 24·0 mg/dL [3·8] in the 400 mg group) and at week 48 (33·7 mg/dL [SE 5·2], 37·1 mg/dL [4·0], and 33·8 mg/dL [4·5]) compared with the tenofovir disoproxil fumarate group (14·5 mg/dL [2·9] and 23·0 mg/dL [3·1] mg/dL). At week 48, mean ratios of total cholesterol to high-density lipoprotein-cholesterol were similar among the BMS-986001 groups (3·5 [SD 1·0] for the 100 mg group, 3·4 [1·1] for the 200 mg group, 3·3 [0·9] for the 400 mg group) and tenofovir disoproxil fumarate (3·6 [1·3]). The appendix shows baseline levels of cholesterol and triglycerides (appendix p 6).

## Discussion

In this study, 24 weeks of treatment with BMS-986001 resulted in a similar number of patients achieving plasma HIV-1 RNA less than 50 copies per mL as did treatment with tenofovir disoproxil fumarate. Within the BMS-986001 groups, antiviral efficacy for the 400 mg group was higher than for the 100 mg and 200 mg groups. At week 48, in the modified intention-to-treat population, BMS-986001 dose-dependent efficacy was recorded, and the 400 mg group showed the greatest efficacy across all treatment groups, including the tenofovir disoproxil fumarate group.

More patients developed emergent resistance to study drugs across all the BMS-986001 groups than in the tenofovir disoproxil fumarate group; the BMS-986001 100 mg group had the highest proportion of patients who developed emergent resistance to study drugs. We speculate that the lower intracellular half-life of the active triphosphate form of BMS-986001 (about 9·7 h)[21] compared with the intracellular half-life of the active diphosphate form of tenofovir disoproxil fumarate (>60 h)[22] might have led to the resistance pattern observed. Additionally, patients randomly assigned to receive BMS-986001 took six pills a day whereas patients in the tenofovir disoproxil fumarate group took three pills a day. This difference in pill burden might have affected adherence; however, we did not formally assess this effect. Importantly, the emergent resistance we noted was mainly to efavirenz and lamivudine. This finding is in line with results from a previous randomised trial (ACTG 5202), which assessed the efficacy, safety and resistance profile of four regimens (ritonavir-boosted atazanavir or efavirenz, both combined with abacavir plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine) in treatment-naive patients. In the ACTG 5202 trial, both NRTI and NNRTI resistance-associated mutations were more common in patients who received efavirenz than in those who received atazanavir plus ritonavir.[23] In a separate randomised trial (SINGLE), which compared dolutegravir plus abacavir plus lamivudine and efavirenz plus emtricitabine plus tenofovir disoproxil fumarate, no patients in the dolutegravir plus abacavir plus lamivudine group had detectable antiviral resistance whereas one tenofovir-associated mutation and four efavirenz-associated mutations were detected in the efavirenz plus tenfovir plus emtricitabine group.[24]

BMS-986001 was generally well tolerated through week 48. Some grade 2–4-related adverse events were more common in the BMS-986001 groups than in the tenofovir disoproxil fumarate group; however, we noted no dose-related trends for the BMS-986001 groups.

In view of the importance of toxic effect issues associated with NRTIs, including decreased bone mineral density,[3] renal dysfunction, lipoatrophy,[4,5] dyslipidaemia, and mitochondrial toxicity,[4,5] we assessed each of these parameters during this study. Compared with the BMS-986001 groups, the decrease in lumbar spine and hip bone mineral density in the tenofovir disoproxil fumarate group was about 2·5-fold greater. This finding is consistent with several other studies,[25,26] which have shown a greater decrease in bone mineral density when using tenofovir-based treatments, compared with other regimens. Reassuringly, changes in bone mineral density noted with BMS-986001 were similar to those reported with abacavir (combined with lamivudine and efavirenz)[25] and recently with tenofovir alafenamide fumarate.[27] Consistent with the smaller decreases in lumbar spine and hip bone mineral density, the changes from baseline for biomarkers of bone resorption and formation were also lower in the BMS-986001 groups compared with tenofovir disoproxil fumarate, suggesting that BMS-986001 has less pronounced effects on the bone. We did not observe substantial changes in creatinine clearance across any treatment group at week 48, although longer-term studies would be needed to establish whether larger changes arise with more prolonged use.

We noted increases in limb and trunk fat for all BMS-986001 and tenofovir disoproxil fumarate groups, with the greatest gains reported in the BMS-986001 400 mg once a day group. Increases in subcutaneous adipose tissue and visceral adipose tissue were seen mainly in the BMS-986001 groups, especially the 400 mg once a day group, and not with tenofovir disoproxil fumarate. The clinical significance of these gains in peripheral and central fat for BMS-986001, particularly for the 400 mg once a day group, will require further study and mechanistic understanding given that visceral fat accumulation has been generally associated with both insulin resistance and cardiovascular disease.[28] Furthermore, the fat accumulation recorded after 48 weeks in this study is similar to that seen after 96 weeks in two other ART-initiation studies using either abacavir with lamivudine or tenofovir disoproxil fumarate with emtricitabine.[29,30] The loss of baseline limb fat (of at least 10%) reported in some patients in this study was generally low for the BMS-986001 groups and the loss of baseline limb fat (of at least 20%) and was similar to that seen with tenofovir disoproxil fumarate. These data for BMS-986001 are similar to findings from other studies with regimens containing abacavir or tenofovir disoproxil fumarate.[29,30] The clinical significance of the small differences in lipid levels between BMS-986001 and tenofovir disoproxil fumarate is unclear and needs longer-term study.

BMS-986001 is an analogue of stavudine, which has been associated with mitochondrial toxicity;[31] therefore, changes in mtDNA copy number were monitored. We noted no meaningful changes from baseline in mtDNA copy number, consistent with the lack of lipoatrophy reported, for BMS-986001. Findings were similar for tenofovir disoproxil fumarate.

Our study had several strengths. The study was done across six continents and women were well represented. Resistance data, including those beyond the week 48 database lock, was included within the analysis of the study. Additionally, thorough safety assessments (bone, metabolic, renal, and mitochondrial safety) were done as part of the study. However, our study also had limitations. Only 18% of patients had baseline HIV-1 RNA of at least 100 000 copies per mL, making it difficult to draw conclusions about this subset of patients. This was also a partly-blinded study, with both patients and investigators masked to BMS-986001 dose, but not allocation. Adherence was also not formally assessed; therefore, any potential effect of pill burden on the observed resistance profile could not be established. Finally, a greater study

size would be required to convincingly show non-inferior efficacy and safety of any dose of BMS-986001 compared with tenofovir disoproxil fumarate.

In conclusion, after 48 weeks of treatment, higher doses of BMS-986001 showed similar efficacy to tenofovir disoproxil fumarate (both combined with efavirenz plus lamivudine). BMS-986001 was generally well tolerated, with smaller decreases in bone mineral density noted across the BMS-986001 groups than seen with tenofovir disoproxil fumarate. We found no signals for mitochondrial toxic effects or concerns about lipoatrophy. However, more patients developed resistance to study drugs in the BMS-986001 groups compared with tenofovir disoproxil fumarate. Additionally, gains in both peripheral and central fat accumulation were noted in the BMS-986001 groups, especially with the 400 mg dose, which potentially raises concerns about insulin resistance and cardiovascular disease. In view of these results, AI467003 was terminated after the week 48 secondary endpoint and Bristol-Myers Squibb has discontinued its involvement in the development of BMS-986001. Any future decisions about the development of BMS-986001 will be made by Oncolys BioPharma, which owns the rights to the compound.

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