Lack of a Significant Drug Interaction between Raltegravir and Tenofovir

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Raltegravir is a novel human immunodeficiency virus type 1 (HIV-1) integrase inhibitor with potent in vitro activity (95% inhibitory concentration of 31 nM in 50% human serum). This article reports the results of an open-label, sequential, three-period study of healthy subjects. Period 1 involved raltegravir at 400 mg twice daily for 4 days, period 2 involved tenofovir disoproxil fumarate (TDF) at 300 mg once daily for 7 days, and period 3 involved raltegravir at 400 mg twice daily plus TDF at 300 mg once daily for 4 days. Pharmacokinetic profiles were also determined in HIV-1-infected patients dosed with raltegravir monotherapy versus raltegravir in combination with TDF and lamivudine. There was no clinically significant effect of TDF on raltegravir. The raltegravir area under the concentration time curve from 0 to 12 h (AUC0–12) and peak plasma drug concentration (Cmax) were modestly increased in healthy subjects (geometric mean ratios [GMRs], 1.49 and 1.64, respectively). There was no substantial effect of TDF on raltegravir concentration at 12 h postdose (C12) in healthy subjects (GMR [TDF plus raltegravir-raltegravir alone], 1.03; 90% confidence interval [CI], 0.73 to 1.45), while a modest increase (GMR, 1.42; 90% CI, 0.89 to 2.28) was seen in HIV-1-infected patients. Raltegravir had no substantial effect on tenofovir pharmacokinetics: C24, AUC, and Cmax GMRs were 0.87, 0.90, and 0.77, respectively. Co-administration of raltegravir and TDF does not change the pharmacokinetics of either drug to a clinically meaningful degree. Raltegravir and TDF may be coadministered without dose adjustments.

The worldwide incidence of human immunodeficiency virus type 1 (HIV-1) infection remains considerable. The number of individuals infected with HIV continues to grow, as does the number of deaths due to AIDS (3, 9, 23). Despite advances in the development of treatment for HIV-1 infection, new agents are still needed to address issues of viral resistance and patient nonadherence due to toxicity.

Raltegravir (MK-0518; Merck & Co., Inc.) is an agent in a new class of antiretroviral drugs, the HIV integrase inhibitors, with a novel mechanism of action (10). HIV integrase inserts viral DNA into the cellular DNA of the host cell and thus is essential for viral replication (1, 5, 10). Raltegravir has potent in vitro activity, blocking HIV replication with a 95% inhibitory concentration (IC95) of 31 nM in 50% normal human serum in vitro activity, blocking HIV replication with a 95% inhibitory concentration (IC95) of 31 nM in 50% normal human serum. This article reports the results of an open-label, sequential, three-period study of healthy subjects. Period 1 involved raltegravir at 400 mg twice daily for 4 days, period 2 involved tenofovir disoproxil fumarate (TDF) at 300 mg once daily for 7 days, and period 3 involved raltegravir at 400 mg twice daily plus TDF at 300 mg once daily for 4 days. Pharmacokinetic profiles were also determined in HIV-1-infected patients dosed with raltegravir monotherapy versus raltegravir in combination with TDF and lamivudine. There was no clinically significant effect of TDF on raltegravir. The raltegravir area under the concentration time curve from 0 to 12 h (AUC0–12) and peak plasma drug concentration (Cmax) were modestly increased in healthy subjects (geometric mean ratios [GMRs], 1.49 and 1.64, respectively). There was no substantial effect of TDF on raltegravir concentration at 12 h postdose (C12) in healthy subjects (GMR [TDF plus raltegravir-raltegravir alone], 1.03; 90% confidence interval [CI], 0.73 to 1.45), while a modest increase (GMR, 1.42; 90% CI, 0.89 to 2.28) was seen in HIV-1-infected patients. Raltegravir had no substantial effect on tenofovir pharmacokinetics: C24, AUC, and Cmax GMRs were 0.87, 0.90, and 0.77, respectively. Co-administration of raltegravir and TDF does not change the pharmacokinetics of either drug to a clinically meaningful degree. Raltegravir and TDF may be coadministered without dose adjustments.

The current recommendations for treatment of HIV infection require combination therapy (3, 9, 17, 23), in part to help address the issue of drug resistance (13, 19, 20, 22). Therefore, it is expected that raltegravir will be given in combination with other anti-HIV drugs such as tenofovir disoproxil fumarate (TDF) (Viread [TDF] package insert, 2007 update; Gilead Sciences, Foster City, CA [http://www.fda.gov/cder/foi/label /2007/021356s021,021752s011lbl.pdf; accessed 31 October 2007]). The prodrug TDF is converted in vivo to tenofovir, a nucleotide reverse transcriptase inhibitor eliminated primarily by renal excretion and the molecule measured for pharmacokinetic (PK) assays. Tenofovir has not been characterized as a potent inhibitor or inducer of drug-metabolizing enzymes, but it has been shown in clinical studies to interact with didanosine, atazanavir, and lopinavir-ritonavir via mechanisms that are not entirely clear (Viread [TDF] package insert, 2007 update).

Raltegravir is metabolized predominantly by glucuronidation mediated by the isoenzyme UGT1A1; raltegravir is not a substrate for cytochrome P-450 enzymes (1, 5). Similar to tenofovir, raltegravir does not appear to be an inducer or inhibitor of enzymes involved in drug metabolism (11, 18; Isentress [raltegravir] package insert). Given the characteristics of each drug, there is no a priori reason to expect that there will be a clinically meaningful drug interaction between TDF and raltegravir. However, due to the unanticipated and unexplained drug interactions previously observed with TDF, a clinical assessment of the effects of each drug on the PK of the other is appropriate. This paper describes the results of a two-way drug-drug interaction study between raltegravir and TDF conducted in healthy subjects, as well as an assessment of the PK of raltegravir administered as monotherapy versus in

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combinations with TDF and lamivudine in HIV-1-infected patients. (Portions of the data from healthy subjects were presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy [24], and partial summaries of the data from patients appear in references 14 and 15.)

MATERIALS AND METHODS

Study design. This report describes two clinical studies in which raltegravir was coadministered with TDF. The first study (protocol 008), study A, was an open-label, three-period, single-center study of healthy subjects. In period 1, raltegravir (400 mg) was administered to all subjects every 12 h for 4 days; on day 4, only the morning dose was administered. In period 2, all subjects were administered TDF (300 mg) once daily for 7 days. In period 3, all subjects received both TDF (300 mg once daily) and raltegravir (400 mg every 12 h) for 4 days. There was no washout period between periods 2 and 3. On non-PK sampling days, TDF was administered with food while raltegravir was administered without regard to food. On PK sampling days (period 1, day 4; period 2, day 7; and period 3, day 4), the study drug was administered in the fasted state.

The second study (protocol 004), study B, was an international, 29-site, double-blind, randomized, dose-ranging study in treatment-naive HIV-1-infected patients that included intensive PK sampling in a cohort of patients. Part I of this study consisted of 10 days of twice-daily dosing with either placebo or raltegravir monotherapy at doses of 100, 200, 400, or 600 mg in a total of 35 patients. Thirty of these patients continued into part II of the study, which examined the safety, tolerability, and efficacy of raltegravir versus efavirenz, in combination with tenofovir and lamivudine, for up to 48 weeks. Patients who received raltegravir in part I received the same dosage of raltegravir in part II, and patients who received placebo in part I received efavirenz (600 mg once daily) in part II. All patients in part II also received TDF (300 mg once daily) and lamivudine (300 mg once daily). Further details of parts I and II of this study have been described previously (14, 15).

Subjects. For study A, healthy (HIV negative), nonsmoking, male subjects, aged 18 to 50 years, weighing within ±20% of ideal body weight were eligible for enrollment. General good health was determined from physical examination, laboratory tests, and medical history; subjects with a history of metabolic, endocrine, neurologic, psychiatric, hematologic, oncologic, cardiovascular, gastrointestinal, hepatic, renal, or genitourinary disease were excluded. Two weeks prior to the study start through the poststudy visit, subjects were required not to take medications included carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, gemfibrozil, and herbal remedies (including, but not limited to St. John’s wort and garlic supplements). Other inclusion and exclusion criteria were previously described (15).

Written informed consent was obtained from all subjects prior to study entry. Each protocol was reviewed and approved by the Institutional Review Board or Ethical Review Committee of each participating site and conducted in accordance with the guidelines on good clinical practice and ethical standards for human experimentation based on those of the Declaration of Helsinki.

PK sampling and assays. For study A, in periods 1 and 3, plasma samples for the raltegravir assay were collected at predose on days 1 to 4 (period 1) or 2 to 4 (period 3) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h postdose on day 4. In periods 2 and 3, serum samples were collected for tenofovir assay at predose on days 1 and 5 to 7 (period 2) or days 2 to 4 (period 3) and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h postdose on day 7 (period 2) or day 4 (period 3).

For study B, plasma was collected for raltegravir assay at predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 18 h following the morning dose on day 10 in part I of the study and at the same time points following the morning dose at week 2 in part II of the study.

Raltegravir samples were analyzed using reverse-phase high-pressure liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) in positive ionization mode using an atmospheric pressure chemical ionization interface (API 4000 HPLC-MS/MS; Applied Biosystems, Foster City, CA), as described in reference 16. The lower limit of quantitation was 2 ng/ml, and the assay was linear from 2 to 1,000 ng/ml. The raltegravir assays from study A were performed at Merck Research Laboratories (West Point, PA); similar methods were used at Bioanalytical Systems, Inc. (McMinnville, OR), to assay samples for study B.

Tenofovir quantitation was conducted at Bioanalytical Systems, Inc. (West Lafayette, IN). Tenofovir was removed from heparinized serum by solid-phase extraction. Tenofovir was then separated and detected by a liquid chromatography-mass spectrometry system using a 100- by 4.6-mm ultra HBD column (Restek Corp., Bellefonte, PA) with a mobile phase of 20% acetonitrile-0.1% formic acid. The internal standard was 2-deoxyadenosine-5’-monophosphoric acid monohydrate. The lower limit of quantitation was 5 ng/ml, and the assay was linear from 5 to 500 ng/ml. The mass transitions used were 288.2 to 175.9 (m/z) for tenofovir and 332.0 to 153.9 (m/z) for the internal standard. Two sets of low-, medium-, and high-quality control samples were evaluated with each run. For these quality control samples, interday accuracy was 99.3 to 102.4% and interday precision was 6.7 to 13.2% (coefficient of variation).

PK methods. For plasma raltegravir concentrations and serum tenofovir concentrations, the area under the concentration-versus-time curve (AUC) was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. Actual recorded sampling times were used for these analyses. Peak plasma drug concentration (Cmax), time to Cmax (Tmax), and concentrations at 12 h postdose (C12 [for raltegravir]) and 24 h postdose (C24 [for tenofovir]) were obtained by inspection of the concentration data.

Safety and tolerability. For study A, the safety and tolerability of raltegravir and TDF were assessed by clinical evaluation of vital signs, physical examination, electrocardiograms, and laboratory safety evaluations, including hematology, chemistry, and urinalysis. Adverse experiences (AEs) were monitored throughout the study. The investigator assessed AEs with respect to intensity (mild, moderate, or severe), duration, seriousness (serious or not serious), outcome, and relationship to study drug.

Clinical and laboratory safety evaluations were also included in study B (14, 15).

Statistical methods. The PK parameters Cmax, C12, and AUC from 0 to 12 h (AUC0–12) for raltegravir and C12 and AUC0–24 for tenofovir were natural log transformed, and confidence intervals (CIs) for the means (and for the difference of the means) were constructed on the natural log scale. Exponentiation was performed on the means (and mean differences) and lower and upper limits of the CIs prior to reporting. With the exception of Tmax, all CIs were based on an analysis of variance (ANOVA) model with treatment as a fixed effect and with the subject as a random effect (with compound symmetric covariance structure assumed). For C12 and C24, only those values arising from the final dosing interval of each period were included in the ANOVA model. All PK parameters were analyzed in separate models. Ninety-five percent CIs were constructed for the geometric means (GMs) of raltegravir C12, Cmax, and AUC0–12 for each treatment regimen, and 90% CIs were constructed for the respective GM ratios (GMRs [raltegravir plus TDF versus raltegravir alone]). For Tmax, the Hodges-Lehman estimate of the true median difference [raltegravir plus TDF − raltegravir alone] was computed, as was a 90% CI for the true median difference. Similar methods were used for analysis of the tenofovir PK parameters.

RESULTS

Subject demographics and baseline characteristics. In study A, 10 men with a mean age of 31.4 years (range, 18 to 43 years) and a mean weight of 81.4 kg (range, 61.4 to 90.0 kg) were enrolled. The racial composition of this group was Hispanic (n = 7), white (n = 2), and black (n = 1). One subject discontinued due to a laboratory AE. Nine subjects completed the study and were included in the PK analysis. All 10 subjects were included in the safety evaluation.

In study B, 30 patients completed the PK substudy; of these, 25 were in treatment arms containing raltegravir and were included in the PK analyses described here. These 25 patients (24 men and 1 woman) had a mean age of 40.6 years (range, 22 to 68 years), a mean weight of 75.7 kg (range, 56.8 to 101.6 kg), and a racial composition of white (n = 16), Hispanic (n = 7), and black (n = 2).

PK of raltegravir. Figure 1 shows the arithmetic mean plasma raltegravir concentration-versus-time profile after multiple-dose administration of raltegravir alone and in combination with multiple-dose TDF in both healthy subjects and treat-
ment-naive HIV-1-infected patients. Table 1 displays the raltegravir PK parameters in healthy subjects from study A, and Table 2 shows them in patients from study B. In healthy subjects, raltegravir $C_{12}$ and $T_{\text{max}}$ were essentially unchanged by coadministration with TDF, while AUC0-12 and $C_{\text{max}}$ were increased by approximately 49% and 64%, respectively. In patients, raltegravir $C_{12}$, AUC0-12, and $C_{\text{max}}$ were all increased by approximately 30 to 40% for coadministration of raltegravir plus TDF plus lamivudine compared to raltegravir alone.

**PK of tenofovir.** Figure 2 displays the mean serum tenofovir concentration-versus-time profile, and Table 3 displays the PK parameters of tenofovir after multiple-dose administration of TDF alone and in combination with multiple-dose raltegravir in healthy subjects. Relative to administration of TDF alone, the coadministration of raltegravir with TDF resulted in little change in tenofovir PK with $C_{24}$, AUC0-24, and $C_{\text{max}}$ decreasing by averages of approximately 13%, 10%, and 23%, respectively. There was no substantial effect on $T_{\text{max}}$.

**Safety and tolerability.** In study A, coadministration of multiple doses of raltegravir with multiple doses of TDF was generally well tolerated. No serious clinical AEs were reported. Of the eight clinical and laboratory AEs reported by four subjects, all were considered by the investigator to be nonserious and possibly related to the study drug. The most common AE was headache. All clinical AEs were mild in intensity and transient in nature. One subject was discontinued from the study due to the laboratory AEs of increased levels of both alanine aminotransferase and aspartate aminotransferase. The abnormal lab values, which were recorded after administration of TDF alone in period 2, returned to baseline levels after discontinuation.

In study B, all doses of raltegravir in combination with TDF and lamivudine were well tolerated in patients, and further details have been published previously (14, 15).

**DISCUSSION**

Drug-drug interactions are particularly important considerations in treating HIV-infected populations and can often be problematic (3, 9, 23). TDF is commonly used in anti-HIV regimens and is likely to be coadministered with raltegravir. No interaction between raltegravir and TDF was anticipated based on in vitro, preclinical, or clinical data; however, TDF is associated with other drug interactions of unknown mechanism: for example, with atazanavir (21), didanosine (12), and saquinavir-ritonavir (2). A study of healthy subjects (study A) was thus conducted to examine the safety and tolerability of raltegravir at 400 mg twice daily alone and in combination with TDF at 300 mg once daily as well as to examine the effects of coadministration on the PK of raltegravir and tenofovir. In addition, the PK of raltegravir were examined in a small cohort

![Fig. 1](image-url)

**FIG. 1.** Arithmetic mean plasma raltegravir concentrations following multiple doses of raltegravir (RAL) at 400 mg twice daily with and without coadministration of multiple doses of TDF alone at 300 mg once daily or TDF at 300 mg once daily plus lamivudine (3TC) at 300 mg once daily. (A) Healthy young men ($n = 9$ [inset, semilog scale]). (B) Treatment-naive HIV-positive patients ($n = 6$ [inset, semilog scale]).

**TABLE 1.** Comparison of plasma raltegravir PK for healthy young men administered multiple doses with and without coadministration of multiple doses of TDF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{12}$ (nM)$^a$</th>
<th>AUC0-12 (µM h$^{-1}$)$^b$</th>
<th>$C_{\text{max}}$ (µM)$^b$</th>
<th>$T_{\text{max}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir alone (95% CI)</td>
<td>142.3 (86.0–35.5)</td>
<td>10.29 (6.56–16.13)</td>
<td>2.87 (1.75–4.71)</td>
<td>1.5$^c$</td>
</tr>
<tr>
<td>Raltegravir + tenofovir (95% CI)</td>
<td>146.4 (88.5–242.4)</td>
<td>15.35 (9.79–24.07)</td>
<td>4.71 (2.87–7.72)</td>
<td>3.0$^d$</td>
</tr>
<tr>
<td>Raltegravir + tenofovir-raltegravir ratio (90% CI)</td>
<td>1.03 (0.73–1.45)</td>
<td>1.49 (1.15–1.94)</td>
<td>1.64 (1.16–2.32)</td>
<td>1.0 (–0.3–1.8)$^d$</td>
</tr>
</tbody>
</table>

| $P$                           | 0.879              | 0.023                     | 0.029                    | 0.281               |

$^a$ Subjects were administered multiple doses of raltegravir (400 mg twice daily) with and without coadministration of multiple doses of TDF (300 mg once daily).

$^b$ The GM was computed from the least-squares estimate from an ANOVA performed on the natural-log-transformed values.

$^c$ Median reported for $T_{\text{max}}$.

$^d$ Hodges-Lehman estimate of median treatment difference and 90% CI for true median treatment difference.
of patients in a study in treatment-naive HIV-1-infected pa-
tients (study B) when administered as monotherapy versus in
combination with TDF at 300 mg once daily and lamivudine at
300 mg once daily.

In both healthy subjects and HIV-1-infected patients, TDF
modestly increased the steady-state raltegravir AUC (in-
creased by 49% in study A) and $C_{\text{max}}$ (increased by 64% in
study A). The mean effect of TDF on steady-state raltegravir
$C_{12}$ differed between the two studies, with essentially no effect
in healthy subjects and an approximately 40% increase in pa-
tients. In study B, raltegravir was dosed in combination with
tenoforvir and lamivudine in part II; raltegravir was adminis-
tered alone in part I.

Raltegravir is an agent in a new class of antiretroviral agents,
and there are insufficient clinical data at this time to defini-
tively say which PK parameters are most important in deter-
mining efficacy and safety. For other classes of antiretroviral
agents, however, there is a reasonable but imperfect associa-
tion of efficacy with trough drug concentration ($C_{\text{trough}}$) values
that exceed the protein-adjusted IC95 in the HIV spread assay.
Since the observed effects of tenofovir on raltegravir $C_{12}$ range
from virtually no change (as observed in healthy subjects in
study A) to a modest increase (as observed in patients in study
B), the interaction is unlikely to have a significant impact on
the efficacy of raltegravir. The modest increases seen in ral-
teggravir AUC$_{0–12}$ and $C_{\text{max}}$ values observed in the presence of

FIG. 2. Arithmetic mean serum tenofovir concentrations following
multiple doses of TDF at 300 mg once daily with and without coad-
ministration of multiple doses of raltegravir at 400 mg twice daily in
healthy young men. Inset, semilog scale.
TABLE 3. Comparison of serum tenofovir PK for healthy young men administered multiple doses of TDF with and without raltegravir

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$ (ng/ml)$^b$</th>
<th>$\text{AUC}_{0-24}$ (ng h$^{-1}$/ml)$^b$</th>
<th>$C_{\text{max}}$ (ng/ml)$^c$</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$P$ $^{d}$</th>
<th>GM (CI) for parameter ($n = 9$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir alone (95% CI)</td>
<td>34.4 (28.0–42.3)</td>
<td>1,737 (1,485–2,032)</td>
<td>263 (223–311)</td>
<td>0.5$^5$</td>
<td>0.137</td>
<td>0.067 (0.001–0.883)</td>
</tr>
<tr>
<td>Tenofovir + raltegravir (95% CI)</td>
<td>29.9 (24.3–36.8)</td>
<td>1,563 (1,326–1,829)</td>
<td>202 (171–239)</td>
<td>1.0$^6$</td>
<td>0.077</td>
<td>0.90 (0.82–0.99)</td>
</tr>
<tr>
<td>Tenofovir + raltegravir-tenofovir ratio (90% CI)</td>
<td>0.87 (0.74–1.02)</td>
<td>0.90 (0.82–0.99)</td>
<td>0.77 (0.69–0.85)</td>
<td>0.3 (0.0–0.8)$^4$</td>
<td>0.87 (0.74–1.02)</td>
<td>0.90 (0.82–0.99)</td>
</tr>
</tbody>
</table>

$^a$ Subjects were administered multiple doses of TDF at 300 mg once daily with and without raltegravir at 400 mg twice daily.

$^b$ The GM was computed from the least-squares estimate from an ANOVA performed on the natural-log-transformed values.

$^c$ Median reported for $T_{\text{max}}$.

$^d$ Hodges-Lehman estimate of median treatment difference and 90% CI for true median treatment difference.

tenofovir are also unlikely to be of concern given the lack of safety issues associated with exposure and maximum plasma drug concentrations seen to date (6–8, 11, 14, 15, 18 Isentress [raltegravir] package insert). Of particular note, the coadministration of raltegravir (400 mg twice daily) with TDF (300 mg once daily) and lamivudine (300 mg once daily) has shown good safety and efficacy in HIV-1-infected patients on long-term dosing (14). These collective data support that the observed effect of tenofovir on raltegravir PK is not clinically significant and that no dose adjustment is needed for raltegravir when it is coadministered with TDF.

As anticipated based on preclinical and in vitro data, raltegravir had no substantial effect on tenofovir PK. Multiple-dose coadministration of TDF and raltegravir led to a slight decrease in mean tenofovir $C_{\text{max}}$ with less of an effect on tenofovir $\text{AUC}_{0-24}$. There was no meaningful effect on tenofovir $C_{\text{max}}$. The effect of raltegravir on tenofovir is similar in magnitude to the reported slight decrease in tenofovir PK parameter values observed on codosing of rifampin with TDF (4). No dose adjustment is recommended for TDF when it is coadministered with rifampin (Viread [tenofovir disoproxil fumarate] package insert, 2007 update), which implies that the observed effect of raltegravir on TDF is also of no clinical significance.

The administration of raltegravir in combination with TDF was generally well tolerated, with no particular safety issue of concern. Present anti-HIV therapies, including nucleoside and nonnucleoside reverse transcriptase inhibitors and protease inhibitors, have toxicity and tolerability issues (3, 9, 23). Raltegravir, an HIV integrase inhibitor, is a member of a new class of antiretroviral agents. Prior clinical experience with raltegravir (6–8, 11, 14, 15, 18; Isentress [raltegravir] package insert), in conjunction with safety data from this study, demonstrates a favorable safety profile and indicates that raltegravir may not have the same toxicity and tolerability issues associated with currently marketed agents.

In summary, the results of this study indicate that coadministration of raltegravir and TDF is generally safe and well tolerated and does not alter the PK of either raltegravir or tenofovir to a clinically meaningful extent, indicating that raltegravir and TDF may be coadministered without dose adjustment.

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Other than employees of Merck & Co., Inc., all authors have been investigators for the sponsor. Employees may hold stock and/or stock options in the company.

K. Lasseter performed the enrollment of subjects and/or data collection, analysis and interpretation of data, and preparation of the manuscript. S. Breidinger, E. Friedman, and J. Stek performed analysis and interpretation of data and preparation of the manuscript. K. Gottestedener, J. Chen, M. Iwamoto, J. Kost, J. Stone, H. Tepler, J. Wagner, and L. Wenning contributed to the study concept and design, analysis and interpretation of data, and preparation of the manuscript.

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