Pharmacokinetics and Pharmacodynamics of Once-Daily versus Twice-Daily Raltegravir in Treatment-Naïve HIV-Infected Patients

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QDMRK was a phase III clinical trial of raltegravir given once daily (QD) (800-mg dose) versus twice daily (BID) (400 mg per dose), each in combination with once-daily coformulated tenofovir-emtricitabine, in treatment-naïve HIV-infected patients. Pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) analyses were conducted using a 2-step approach: individual non-model-based PK parameters from observed sparse concentration data were determined, followed by statistical analysis of potential relationships between PK and efficacy response parameters after 48 weeks of treatment. Sparse PK sampling was performed for all patients (QD, \( n = 380 \); BID, \( n = 384 \)); selected sites performed an intensive PK evaluation at week 4 (QD, \( n = 22 \); BID, \( n = 20 \)). In the intensive PK subgroup, daily exposures (area under the concentration-time curve from 0 to 24 h \([\text{AUC}_{0–24}]\)) were similar between the two regimens, but patients on 800 mg QD experienced ~4-fold-higher maximum drug concentration in plasma (\( C_{\text{max}} \)) and ~6-fold-lower trough drug concentration (\( C_{\text{trough}} \)) values than those on 400 mg BID. Geometric mean (GM) \( C_{\text{trough}} \) values were similarly lower in the sparse PK analysis. With BID dosing, there was no indication of any significant PK/PD association over the range of tested PK parameters. With QD dosing, \( C_{\text{trough}} \) values correlated with the likelihood of virologic response. Failure to achieve an HIV RNA level of <50 copies/ml appeared predominantly at high baseline HIV RNA levels in both treatment arms and was associated with lower values of GM \( C_{\text{trough}} \) in the 800-mg-QD arm, though other possible drivers of efficacy, such as time above a threshold concentration, could not be evaluated due to the sparse sampling scheme. Together, these findings emphasize the importance of the shape of the plasma concentration-versus-time curve for long-term efficacy.

MATERIALS AND METHODS
QDMRK (MK-0518 protocol 071; NCT00745823) was a phase III noninferiority study in treatment-naïve HIV-1-infected adults that evaluated the safety and efficacy of raltegravir given as an 800-mg dose once daily versus the approved regimen of 400 mg twice daily, both given with once-daily coformulated tenofovir at 300 mg plus emtricitabine at 200 mg. Details regarding patient selection, treatment assignment, and virologic assays have been previously described (6).

Pharmacokinetic and pharmacodynamic studies. Sparse PK sampling was performed for all patients (\( n = 380 \) [QD arm] or 384 [BID arm]). One plasma sample was collected at weeks 2, 4, 8, 12, 16, 24, and 48; these samples were collected predose at weeks 4, 8, 24, and 48 and irrespective of dosing time at other visits. At each visit, the study coordinator recorded details of the patient’s food intake surrounding their last dose of study therapy, specifically whether they had no food, a light meal, a moderate meal, or a full meal within 2 h before or within 1 h after taking the study drug. The exact time of the dose taken prior to collection of the
sparse PK sample and the exact time the sparse PK sample was drawn were also recorded. Selected sites performed an intensive PK evaluation at week 4 and therefore did not collect sparse PK samples at this visit (n = 22 [QD arm] or 20 [BID arm]). For the intensive PK evaluation, no specific instructions were given with regard to food intake around the time of dosing. However, for the same visit during which the intensive PK samples were drawn, patients were instructed to be in a fasted state for the collection of blood samples for safety labs. Thus, it is likely that the majority of intensive PK was collected in the fasted state. Samples were collected at the following time points: Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h postdose.

**Determination of raltegravir concentrations in plasma.** Plasma samples were analyzed for raltegravir concentrations at PharmaNet Canada, Inc. (Quebec, Canada). The analytical method for the determination of raltegravir in human plasma involves isolation, via 96-well liquid-liquid extraction, of the analyte and internal standard from plasma, followed by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) analysis. The lower limit of quantitation (LLOQ) for the plasma assay was 2 ng/ml (4.5 nM), and the linear calibration range was 2 to 1,000 ng/ml. More details regarding the bioanalysis can be found in the previously published methods (16).

**Pharmacokinetic analyses.** For the subset of patients with intensive PK profiles collected at week 4, a noncompartmental analysis was conducted using the software program WinNonlin to calculate the area under the concentration-time curve from 0 to 24 h (AUC_{0–24}), the concentration of drug in plasma at 12 h and maximum drug concentration (C_{max} and C_{max}), and the time to maximum concentration of drug in plasma (T_{max}) for patients in the BID treatment arm or AUC_{0–24}, C_{max}, and T_{max} for patients in the QD treatment arm. The linear up/log down method was used for AUC calculation, and actual elapsed times postdose were used for the analysis. Due to the large degree of interoccasion variability in the absorption of raltegravir, a population PK model could not be developed, and so traditional PK parameters, such as AUC and C_{max}, could not be derived from modeling of the sparse sampling data (3) and could be assessed only in the subset of patients with intensive PK profiles collected at week 4. The PK parameters used for this analysis for the entire treatment population were calculated for the interval from week 0 to week 48 using the observed sparsely collected PK samples only. These PK parameters include the following.

- **GM C_{trough} (C_{12} for BID dosing; C_{4} for QD dosing).** The geometric mean (GM) was defined as the geometric mean of all samples for a particular patient collected between 11 and 13 h postdose (for GM C_{12}) or between 22 and 26 h postdose (for GM C_{4}). This parameter was examined because response to antiretroviral therapies is often thought to be driven by trough drug concentrations in plasma (C_{trough}). At weeks 4, 8, 24, and 48, PK samples were drawn prior to the morning dose, which aimed to provide an adequate number of samples to capture the trough plasma concentration for both QD and BID dosing and allow for calculation of a geometric mean. Additional samples collected without respect to time may also add to the number of samples falling between the defined time windows postdose.

- **C_{min}.** The geometric mean of all observed concentrations (C_{GM}) was defined as the geometric mean of all samples for a particular patient, regardless of when they were collected.

- **C_{min}.** The minimum of all observed concentrations (C_{min}) was defined as the minimum value of all samples for a particular patient, regardless of the time of collection. Based on analyses of the intensive sampling data from phase I and II studies, a high prevalence of secondary peaks was observed, indicating that samples within the defined window for trough concentrations may miss the true minimum concentration. This measure will assess the impact of particularly low observed concentrations in plasma.

Summary statistics (geometric mean with percent coefficient of variation [95% CI]) were calculated for both the sparse PK parameters (GM C_{12} or GM C_{4}, C_{trough}, and C_{min}) and the intensive PK parameters (AUC_{0–24} or AUC_{0–12} or C_{12} or C_{4}, C_{max}, and T_{max}) for each treatment arm of the study (BID or QD). AUC parameters (AUC_{0–12} for BID and AUC_{0–24} for QD) were analyzed using a one-way analysis-of-variance (ANOVA) model containing a single factor of treatment (BID or QD). PK parameters were transformed in the natural log scale before analysis and back transformed for reporting. The geometric mean ratio (GMR) estimate (2 × AUC_{0–12} for BID versus AUC_{0–24} for QD) and 90% confidence interval (CI) were also calculated. Similar analyses were performed for C_{trough}.

**PK/PD analyses.** The analyses described below were conducted on 3 data sets: (i) BID arm alone, (ii) QD arm alone, and (iii) BID and QD arms pooled. Logistic regression models were used to explore the PK/PD association between the various PK parameters and the proportion of patients with HIV RNA levels of <50 copies/ml at week 48, HIV RNA levels of <400 copies/ml at week 48, and the occurrence of virologic failure. In this study, virologic failure was defined as having an HIV RNA level of >50 copies/ml at week 24 of the study and virologic relapse was defined as an HIV RNA level of >50 copies/ml on two consecutive measurements at least 1 week apart after an initial response defined by an HIV RNA level of <50 copies/ml. All PK/PD analyses used the observed failure (OF) approach for the various PD endpoints; the OF approach counts as failures only those patients who discontinue due to lack of efficacy, and it therefore considers only the virologic effect of treatment. In addition to using the PK parameter of interest (in log_{10} scale) as the explanatory variable, the baseline HIV RNA level (log_{10} copies/ml) was included in the logistic regression model. Covariates such as age and gender were not included in the model, since they have been found to be noninfluential in previous analyses of raltegravir PK (3) and not significant prognostic factors in previous phase II and III efficacy analyses (17, 20). The estimated odds ratio with 95% CI and the associated P value for the association between each sparse PK parameter and each PD parameter were calculated. The odds ratio coefficient resulting from the regression model can be interpreted as the fold change in the odds (probability of the event occurring over the probability of the event not occurring) of the response for each 1-unit increase on the log_{10} scale in the PK parameter. A similar logistic regression model was applied to the analysis on the occurrence of virologic failure. To graphically represent the observed PK/PD relationships, the probability of achieving the efficacy endpoint was calculated from the following equation: \[ \log[p/(1-p)] = a - (b \times \log_{10} x_i) + (c \times \log_{10} x_i) \], where \( p \) is the probability of achieving the efficacy endpoint (i.e., HIV RNA < 50 copies/ml), \( x_i \) is the baseline HIV RNA level in copies/ml, \( x_i \) is the PK parameter being examined (i.e., GM C_{trough}), and \( a, b, \) and \( c \) are the constants that are fit to the observed data in the logistic regression. Receiver operating characteristic (ROC) curves were also constructed to assess whether using a single threshold of the sparse PK parameter can predict the above-mentioned PD endpoints well. Taking HIV RNA at <50 copies/ml at week 48 as an example, the prediction rule would be that a patient will achieve (or fail to achieve) this criterion if the PK parameter is above (or below) the threshold value. With an ROC curve, sensitivity is plotted against 1-specificity, where sensitivity (or specificity) is defined as the observed proportion of correctly predicted failures (or responder).

**RESULTS**

**Pharmacokinetic analyses.** As detailed previously, sparse PK samples were collected for all patients in both arms (400 mg BID and 800 mg QD) of the study, with a subset of patients having intensive PK profiles collected at week 4. In the intensive PK subgroup, daily exposures to raltegravir (AUC_{0–24}) were similar between the two regimens (Table 1), but patients on 800 mg QD experienced approximately 4-fold-higher C_{max} and 6-fold lower C_{trough} values than those on 400 mg BID (Table 1 and Fig. 1). GM C_{trough} values were similarly lower in the analysis of sparse PK data, with geometric mean ratios (GMR) comparing C_{trough} values for the QD versus BID arms of 0.15 (6-fold lower) in the intensive PK data and 0.22 (4.5-fold lower) in the sparse PK data. To examine the effect of food on the pharmacokinetics of raltegravir, indi-
vial concentrations in plasma as a function of the time since last dose, stratified by meal type, were examined for both the QD and BID arms. In the sparse PK sampling data set, there did not appear to be an obvious trend of the influence of meal type on raltegravir plasma concentrations (data not shown). Intensive PK profiles for patients in QDMRK were generally consistent with previous observations of HIV-infected patients (12) and of healthy volunteers (3), where raltegravir concentrations declined from $C_{\text{max}}$ in a biexponential manner with an initial half-life of approximately 1 h and a terminal half-life of approximately 9 h. In both the sparse and intensive PK data sets, the GM $C_{\text{trough}}$ plasma concentrations in both arms of the study exceeded 31 nM, the mean in vitro 95% inhibitory concentration ($IC_{50}$) of raltegravir for wild-type HIV-1 in the presence of 50% normal human serum; however, GM $C_{\text{trough}}$ values for the 800-mg-QD arm of the study were approximately 4.5-fold and 6-fold lower than in the 400-mg-BID arm, respectively, in the sparse and intensive data sets. Additionally, in the 400-mg-BID arm of the intensive PK data set, $C_{\text{trough}}$ values for all subjects exceeded 31 nM. The geometric mean of $C_{\text{min}}$ for both arms of the study in the sparse PK data set also exceeded 31 nM; however, a greater proportion of individuals on 800 mg QD (42.4%) exhibited $C_{\text{min}}$ below 31 nM than individuals on 400 mg BID (13.8%). Nanomolar values can be converted to ng/ml by multiplying by 0.4444 (the molecular weight of raltegravir is 444.4 g/mol). For instance, the above-mentioned IC$_{95}$ of 31 nM is equal to 13.8 ng/ml.

PK/PD analyses. To explore the potential association between sparse PK parameter values and antiretroviral responses for patients receiving raltegravir at 800 mg QD or 400 mg BID, logistic regression models were used to analyze each of 3 data sets: (i) the BID arm alone, (ii) the QD arm alone, and (iii) the BID and QD arms pooled for the association between each sparse PK parameter and each of the response parameters (HIV RNA level of <400 copies/ml at week 48, HIV RNA level of <50 copies/ml at week 48, and virologic failure by week 48). The estimated odds ratios are presented in Table 2. For patients in the BID arm, there was no indication of any significant PK/PD association over the range of tested PK values, which is consistent with prior analyses of PK/PD data after BID administration in the treatment-naive population.

In the analysis of the QD arm, only 1 significant relationship was identified (between $C_{\text{all}}$ and HIV RNA levels of <400 copies/ml); however, consistent trends in the expected direction are observed for each of the PK parameters and virologic endpoints. When data from both arms of the study are pooled, many significant relationships emerge, again trending in the expected direction. The increased degree of significance in the observed PK/PD relationships when both arms are included in the analysis is likely due to a combination of both a higher number of individuals included in the pooled analysis and a wider range of observed PK parameters spanning both the QD and BID arms.

All of the sparse PK parameters examined in this study ($GM_{C_{\text{trough}}}$, $GM_{C_{\text{all}}}$, and $GM_{C_{\text{min}}}$) appear to be associated with efficacy, and as illustrated by the logistic regression results shown in Table 2 and the ROC analysis discussed below, all three parameters appear to

![FIG 1 Arithmetic mean (SE) concentration-time profiles for the subset of patients with intensive PK sampling at week 4. For the intensive PK evaluation, samples were collected at the following time points: predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h postdose.](image-url)

**TABLE 1 Summary pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value for group$^d$</th>
<th>Value for group$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raltegravir QD group</td>
<td>Raltegravir BID group</td>
</tr>
<tr>
<td></td>
<td>No. of patients</td>
<td>GM (% CV)</td>
</tr>
<tr>
<td>Intensive pharmacokinetic profiles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_0-12$ (μM·h)</td>
<td>22</td>
<td>30.87 (70)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (μM)</td>
<td>22</td>
<td>13.46 (69)</td>
</tr>
<tr>
<td>$C_{\text{trough}}$ (nM)</td>
<td>22</td>
<td>40 (111)</td>
</tr>
<tr>
<td>Sparse pharmacokinetic samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{all}}$ (nM)</td>
<td>380</td>
<td>196 (176)</td>
</tr>
<tr>
<td>$GM_{C_{\text{trough}}}$ (nM)</td>
<td>245</td>
<td>83 (140)</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (nM)</td>
<td>380</td>
<td>46 (189)</td>
</tr>
</tbody>
</table>

$^a$ AUC$_{0-24}$ was determined for the BID arm, and AUC$_{0-12}$ was determined for the QD arm. The ratio is for 24-h exposure: AUC$_{0-24}$ QD/(2 × AUC$_{0-12}$ BID).

$^b$ $C_{\text{trough}} = C_{\text{all}}$ for BID and $C_{\text{trough}}$ for QD.

$^c$ $GM_{C_{\text{trough}}}$ was calculated from sparse PK samples using all concentration measurements between 11 and 13 h postdose for a BID recipient or between 22 and 26 h postdose for a QD recipient.

$^d$ GM values were back transformed from log scale. % CV = $100 \times \sqrt{\varepsilon^2} - 1$, where $\varepsilon^2$ is the observed variance on the natural log scale.
be similar in terms of predictive value. Since GM $C_{\text{trough}}$ is the parameter most similar to a traditional PK parameter and the one that would be easiest to measure in a clinical context, further analyses and discussion focus on this parameter.

The graphical description of the PK/PD relationship between GM $C_{\text{trough}}$ and the probability of achieving an HIV RNA level of $<50$ copies/ml stratified by log$_{10}$ baseline HIV RNA for the QD treatment arm shows the expected trend, that a higher GM $C_{\text{trough}}$ value increases the probability of achieving an HIV RNA level of $<50$ copies/ml (Fig. 2). This relationship is also evident when examining the data arranged by quartiles of the GM $C_{\text{trough}}$ data and the percentage of patients in each quartile that achieved an HIV RNA level of $<50$ copies/ml, where there is an observed drop-off in efficacy for patients in the 800-mg-QD arm of the study in the lowest quartile of GM $C_{\text{trough}}$ (Fig. 2).

As an alternative method of examining the multivariate influence of both PK and the baseline viral load on the antiviral response, GM $C_{\text{trough}}$ is plotted against the log$_{10}$ of baseline HIV RNA, with different symbols representing the QD and BID arms of the study, and if the patient did or did not achieve HIV RNA levels of $<50$ copies/ml (Fig. 3). Results of this analysis indicate that in both treatment arms, failure to achieve an HIV RNA level of $<50$ at wk 48 is largely determined by the GM $C_{\text{trough}}$ value, range of GM $C_{\text{trough}}$ and stratified by log baseline HIV RNA for the QD treatment arm (solid) and the 25% and 75% quartiles (dashed). Probability curves are superimposed above observed data (divided by quartiles) for the GM $C_{\text{trough}}$ and the percentage of patients observed with HIV RNA levels of $<50$ copies/ml. The median GM $C_{\text{trough}}$ value, range of GM $C_{\text{trough}}$ values in the quartile, number of subjects achieving HIV RNA levels of $<50$ copies/ml, and total number of subjects in each quartile are displayed below each quartile.
baseline HIV RNA provides the best separation between true-positive (sensitivity) and false-positive (1 − specificity) results, yielding better separation than any of the PK parameters examined. Specifically, the ROC analysis resulted in a threshold value of 4.90 for the log_{10} baseline HIV RNA, corresponding to a baseline viral load of approximately 80,000 copies/ml. These results indicate that there is not a specific value of any of the PK parameters examined that provides a threshold for virologic response. Other possible drivers of efficacy, such as the time above a threshold concentration, could not be evaluated from this data set due to the sparse PK sampling scheme employed for the majority of patients in the study and the small number of virologic failures within the intense PK subgroup. Specifically, 3 patients in the QD arm and 1 patient in the BID arm of the intense PK subgroup experienced virologic failure.

**DISCUSSION**

In this study of raltegravir given once daily versus twice daily, failure to achieve an HIV RNA level of <50 copies/ml appeared predominantly at high baseline HIV RNA levels in both treatment arms and was also associated with lower values of GM $C_{\text{trough}}$ in the 800-mg-QD arm. The patients with the greatest risk of failure were those with a combination of high baseline HIV RNA and low GM $C_{\text{trough}}$ in the 800-mg-QD arm. The patients with the greatest risk of failure were those with a combination of high baseline HIV RNA and low GM $C_{\text{trough}}$ (Fig. 3). These findings are consistent with results of the ROC analysis, which also identified the baseline viral load as the parameter best associated with providing a threshold for the greatest degree of both sensitivity and specificity in efficacy. Although none of the raltegravir PK parameters examined yielded sensitive or specific threshold values, they were also significantly associated with efficacy in a logistic regression analysis that accounted for the effect of baseline HIV RNA. With the current data set, correlations are seen between efficacy and several summary measures of raltegravir PK, including trough concentrations, but we cannot evaluate other possible drivers of efficacy, such as the time above a threshold concentration, due to the sparse PK sampling scheme employed for the majority of patients in the study and the small number of virologic failures within the intense PK subgroup. The observation of only a slight drop-off in efficacy with QD treatment (83% versus 89%) (6) corresponding with a severalfold drop in $C_{\text{trough}}$ suggests that BID administration of raltegravir results in $C_{\text{trough}}$ values well along the exposure-response plateau and that the pharmacokinetics of this regimen are above the minimum required for efficacy. However, the QD arm of the study was inferior to the BID arm in the context of similar daily exposures, implying that the shape of the PK curve is important for the long-term efficacy of raltegravir and that the maintenance of raltegravir levels throughout the dosing interval is important for efficacy.

Results from the intensive pharmacokinetic analysis in a subgroup of patients in each treatment arm of the QDMRK study indicated that total daily exposures were similar between once-daily and twice-daily regimens; however, administration of raltegravir at a once-daily dose of 800 mg resulted in a different shape to the PK profile than the administration of 400 mg twice daily. Specifically, QD dosing resulted in a higher peak-to-trough ratio, with 4-fold-higher $C_{\text{max}}$ and 6-fold lower $C_{\text{trough}}$ values relative to those for 400 mg BID. Analysis of sparsely sampled PK data from all patients in the study confirmed this observation, since GM $C_{\text{trough}}$ values were similarly lower (4.5-fold) when comparing data from the QD arm relative to those from the BID arm.

PK/PD analyses of patients in the BID arm of the study revealed...
no indication of significant PK/PD associations over the range of
tested PK parameter values. In contrast, analysis of data from the
QD arm revealed an apparent association between PK and viro-
logic outcome measures; however, no clear threshold value for any
of the PK parameters could be identified (Fig. 4). Whether the
most important parameter is $C_{\text{min,G}}$, $C_{\text{trough}}$, or $C_{\text{all}}$ cannot be
determined using the data from this study; further analyses and
discussion focus on GM $C_{\text{trough}}$ since this is the parameter most
likely to be of use clinically. Examination of the QD arm data
grouped by quartiles showed a drop-off in the lowest quartile of
$C_{\text{trough}}$ with respect to efficacy. Patients in this lowest quartile had a
mean $C_{\text{trough}}$ value of 28.2 nM, with a range from 7.1 to 43.3 nM.
Note that this mean $C_{\text{trough}}$ value is just below 31 nM, the mean in
vitro IC$_{50}$ of raltegravir for wild-type HIV–1 in the presence of 50% normal human serum. Similar trends were not observed for the
BID arm when the quartiles of $C_{\text{trough}}$ data were examined, con-
sistent with the observation that the values of raltegravir PK pa-
rameters in the highest QD arm quartile are similar to those in the
lowest BID arm quartile. Specifically, in the QD arm, the mean $C_{\text{trough}}$ values in the two highest quartiles were 100 and 245 nM,
while in the BID arm the mean $C_{\text{trough}}$ values in the two lowest quartiles were 135 and 293 nM. These results are consistent with find-
tings for the investigational integrase inhibitors elvitegravir (5) and
dolutegravir (18), where it has been reported that efficacy is cor-
related with $C_{\text{trough}}$.

The lack of a significant PK/PD association coupled with the high
response rate of 89% observed for the BID arm indicates that key PK parameter values are likely above the minimum required for
efficacy. As observed in previous studies (2, 9, 12, 15, 22), the high
degree of variability in the observed raltegravir pharmacoki-
netics, both interoccasion and interindividual, precludes the use of
therapeutic drug monitoring for twice-daily dosing of the cur-
rently marketed formulation.

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