Lack of an Effect of Human Immunodeficiency Virus Coinfection on the Pharmacokinetics of Entecavir in Hepatitis B Virus-Infected Patients^\textsuperscript{7}

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Entecavir is a guanosine nucleoside analogue approved for the treatment of chronic hepatitis B virus (HBV) infection. The impact of human immunodeficiency virus (HIV) coinfection on the pharmacokinetics (PK) of entecavir was examined by nonlinear mixed-effects modeling. Plasma concentration data from HIV- and HBV-coinfected patients were analyzed in conjunction with data from HBV-monoinfected patients, and HIV coinfection was tested as a covariate on oral clearance (CL/F). The estimated population averages of intercompartmental clearance and the volumes of distribution in the central and peripheral compartments obtained with a 1-mg dose were 34.2 liters/h (interindividual variability, 30.2%), 115 liters (interindividual variability, 39.2%), and 1,830 liters (interindividual variability, 74%), respectively. CL/F was found to be a function of creatinine clearance, but HIV coinfection did not show any effect on CL/F. The geometric mean (GM) of individual Bayesian estimates of the steady-state area under the concentration-time curve following 1-mg daily doses were 39.3 and 38.8 ng · h/ml in HIV- and HBV-coinfected and HBV-monoinfected patients, respectively. The adjusted GM ratio (1.01; 90% confidence interval, 0.91 to 1.12) was within the bioequivalence criteria boundary (0.80 to 1.25). In conclusion, the proposed model adequately described the entecavir PK in HBV- and HBV-coinfected patients and HBV-monoinfected patients, and the entecavir exposures were comparable in the two patient populations.

Up to 370 million people in the world are chronically infected with hepatitis B virus (HBV), and approximately 40 million individuals are infected with human immunodeficiency virus (HIV) (15, 34). Approximately 10% of HIV-infected individuals are coinfected with HBV (29) as a result of the common transmission routes of the two viruses. Published data in 2002 suggested that the liver-related mortality rate was higher in HIV- and HBV-coinfected patients (14.2/1,000 person years) than in HIV type 1 (HIV-1)-monoinfected patients (1.7/1,000 person years) (33).

The clinical management of patients with HIV and HBV coinfection is particularly challenging due to interactions between both infectious processes and their treatments (6, 12, 14, 31, 32). The main focus of current therapies is to suppress viral replication and to achieve a subsequent improvement in immune function and a decrease in hepatic necroinflammatory disease. The available treatment options and experience with the management of HIV and HBV coinfection are still limited. Although lamivudine is recommended for the treatment of HIV and HBV coinfection due to its activity against both viruses, the rapid development of lamivudine resistance in patients infected with both HIV and HBV has been found to be a major concern (12, 31, 32).

Entecavir is a potent guanosine nucleoside analogue approved for use for the treatment of chronic HBV infection in adults (28; entecavir package insert; Pharmaceutical Research and Development, Bristol-Myers Squibb Company). Entecavir is efficiently phosphorylated to the active triphosphate form, which inhibits all three activities of the HBV polymerase: base priming, reverse transcription of the negative strand from the pregenomic mRNA, and synthesis of the positive strand of HBV DNA. To evaluate the anti-HBV effect of entecavir in HIV- and HBV-coinfected patients, a phase II clinical trial (study AI463-038) was conducted with HIV- and HBV-coinfected patients who experienced a recurrence of HBV viremia while they were receiving lamivudine-containing highly active antiretroviral therapy (HAART) (25, 26). Plasma entecavir concentrations were measured throughout the study.

This report presents the results of a population pharmacokinetic (PK) analysis of entecavir in HIV- and HBV-coinfected patients and an evaluation of the impact of HIV and HBV coinfection on the PKs of entecavir. Since model-based pooled analysis is an effective means of characterization of PKs in different patient populations (2), plasma entecavir concentration data for HIV- and HBV-coinfected patients (study AI463-038) were analyzed simultaneously with data for HBV-monoinfected patients derived from three phase II clinical trials, studies AI463-004, AI463-005, and AI463-014 (7, 10, 18).

MATERIALS AND METHODS

This section provides a brief description of the study conducted with HIV- and HBV-coinfected patients (study AI463-038) and brief descriptions of the three studies conducted with HBV-monoinfected patients (studies AI463-004, AI463-005, and AI463-014). In addition, the methods for the data analysis are described.

Clinical study with HIV- and HBV-coinfected patients. Study AI463-038 was a randomized, double-blind, placebo-controlled, multicenter trial designed to assess the safety and anti-HBV activity of the current lamivudine-containing HAART to which entecavir was added in HIV- and HBV-coinfected patients. The study was approved by the institutional review boards of the participating centers; all subjects gave written informed consent for their participation in the study. Patients had controlled HIV status (HIV RNA load, <400 copies/ml for more than 12 weeks prior to screening) but had HBV viremia (HBV DNA load, \(\geq 10^5\) log\(_{10}\) copies/ml for more than 4 weeks prior to screening, as measured by

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PCR assay) (25). The study included two phases: a 24-week randomized, double-blind, placebo-controlled phase (weeks 1 to 24) and a 24-week open-label entecavir phase (weeks 25 to 48). In the double-blind phase, the subjects were randomized (2:1) to receive entecavir 1.0 mg once daily (QD) or placebo QD. All subjects continued their current HAART containing lamivudine (150 mg twice daily or 300 mg QD) throughout the study. Individuals who completed the 24-week double-blind phase continued the 24-week open-label phase and received entecavir at 1.0 mg QD while they maintained their lamivudine-containing HAART (26).

Plasma samples were collected from 58 HIV- and HBV-coinfected patients for measurement of entecavir concentrations at predosing on day 1 and at 1.5, 3, and 6 h postdosing on a scheduled visit day during week 2. This sampling scheme was close to the scheme selected by the D-optimal design (sampling at the trough and at 0.2, 1.4, 3.5, and 10 h postdosing). Sparse samples were also collected randomly at least 1 h postdosing during weeks 12, 24, 36, and 48. Plasma entecavir concentrations were determined by a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantitation of 0.005 ng/ml (35).

Clinical studies with HBV-monoinfected patients. Data from three clinical trials (studies AI463-004, AI463-005 and AI463-014) with HBV-monoinfected patients were included in this analysis. The analytical method for entecavir was the same as that used in study AI463-038.

Study AI463-004 was a randomized, double-blind, placebo-controlled, dose-escalating study of four doses (0.05, 0.1, 0.5, and 1.0 mg QD) of entecavir. Patients were treated for a period of 28 days with a 24-week follow-up (10). The HBV-infected patients either were treatment naive or had been pretreated with lamivudine-interferon. Trough samples for PK analysis were collected on days 1, 7, 14, 21, and 28 prior to administration of the daily dose of entecavir. Evaluable plasma entecavir concentrations were obtained from 30 patients.

Study AI463-005 was a phase II, randomized, double-blind study of three doses (0.01, 0.1, and 0.5 mg QD) of entecavir given for 24 weeks compared to lamivudine administered at 100 mg QD in patients with chronic HBV infection who were nucleoside treatment naive (lamivudine therapy for 12 weeks or less) (18). Sampling for entecavir PK analysis was performed at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, or 24 h postdosing on day 1 and on weeks 4, 12, 24, 36, and 48 at least 1 h postdosing. Evaluable plasma entecavir concentrations were obtained from 120 patients.

Study AI463-014 was a phase II, randomized, double-blind study of three doses (0.1, 0.5, and 1.0 mg QD) of entecavir compared to lamivudine administered at 100 mg daily in subjects with chronic HBV infection who had documented HBV viremia on two or more occasions while on current lamivudine therapy (7). Study dosing was continued for up to 48 weeks. Sampling for entecavir PK analysis was performed at 1.5, 3, and 6 h postdosing on day 1 and on weeks 4, 12, 24, 36, and 48 at least 1 h postdosing. Evaluable plasma entecavir concentrations were obtained from 72 patients.

PK evaluation. Entecavir is rapidly absorbed after oral administration, with the time to the peak concentration being between 0.5 and 1.5 h (35; entecavir package insert; Pharmaceutical Research and Development, Bristol-Myers Squibb Company). A population PK model was previously developed with data from HBV-monoinfected patients, and creatinine clearance (CLCR) was identified as the only factor that affected entecavir exposure (17). This model was employed in the current analysis, with modifications. Details of the model are described below. Moreover, the model was reevaluated with combined data from the HBV-monoinfected and the HIV- and HBV-coinfected patients, and the effect of infection status (monoinfection versus coinfection) on the PKs of entecavir was tested as a covariate.

The population PK modeling consisted of four steps: (i) creation of the analysis data set, (ii) estimation of the PK parameters, (iii) testing of infection status as a covariate, and (iv) comparison of the entecavir PKs in the two patient groups. A description of each step is given below.

(i) Creation of analysis data set. The final modeling data set consisted of 256 concentration data points from 58 HIV- and HBV-coinfected patients who received 1.0 mg entecavir QD and 1,244 concentration data points from 222 HBV-monoinfected patients who received entecavir monotherapy over a dose range of 0.01 to 1.0 mg QD. The demographics for both patient groups are provided in Table 1. The dose-normalized plasma entecavir concentration-versus-time data are depicted in Fig. 1.

(ii) Estimation of PK parameters. A first-order absorption and two-compartment disposition model was used to describe the PKs of entecavir. The structural model parameters included the absorption rate constant (Ka), apparent oral clearance (CL/F), apparent volumes of distribution in the central (Vc/F) and peripheral (Vp/F) compartments, and intercompartmental clearance (Q/F). Since entecavir is mainly excreted renally, CL/F was expressed as a function of CLCR, the method described by Cockroft and Gault (8). Calculated CLCR values in excess of 150 ml/min were imputed as 150 ml/min (16). In this analysis, CLCR was transformed to the normalized ideal body weight-corrected CLCR (NICRC), and Q/F was described as a function of dose to account for dose-dependent drug distribution. Expressions of the structural model parameters are provided in Equations 1 to 5:

\[ K_a = \theta_1 \] (1)
The residual error for the \( j \)th observation in the \( i \)th individual, \( \varepsilon_{ij} \), is the value predicted by the model, and \( \varepsilon_i \) is a realization of a normally distributed random variable with a mean of 0 and a variance of \( \sigma_i^2 \) given by Equation 7:

\[
\varepsilon_i \sim N(0, \sigma_i^2)
\]

where \( N \) is normal distribution. A residual error model consisted of a proportional and additive component. The residual error for the \( j \)th observation in the \( i \)th individual is described by Equation 8:

\[
y_{ij} = \hat{y}_i(1 + \varepsilon_{ip}) + \varepsilon_{ia}
\]

where \( \hat{y}_i \) is the value predicted by the model, and \( \varepsilon_{ip} \) and \( \varepsilon_{ia} \) represent the proportional and additive residual errors corresponding to the observed value of \( y_{ij} \), respectively. Both \( \varepsilon_{ip} \) and \( \varepsilon_{ia} \) are assumed to be normally distributed random variables with means of 0 and variances of \( \sigma_i^2 \) and \( \sigma_i^2 \), respectively.

The ADVAN4 TRANS4 in NONMEM software (version 5, level 1.1) was used for analysis (3). The first-order conditional estimation with interaction was used to estimate the values of the PK parameters.

### iii) Testing of infection status as a covariate

LRT was used to evaluate the effect of infection as a covariate on \( CL/F \) and to test the significance of reduction in the objective function value (\( \Delta OFV \)):

\[
\Delta OFV = OFV_M1 - OFV_M2
\]

where \( OFV_M1 \) represents the OFV obtained from the fit of a model that accounts for the covariate effect (M1), and \( OFV_M2 \) represents the OFV obtained from the fit of a reference model that does not account for the covariate effect (M2). With LRT, a \( \Delta OFV \) value is approximately chi-squared distributed with \( n \) degrees of freedom. When \( n \) is equal to 1, \( \Delta OFV \) values of 3.84, 6.63, and 10.83 generate statistical significance values of \(<0.05\), \(<0.01\), and \(<0.001\), respectively (27, 30). The significance-of-covariate effect was set at the 0.05 level. If the value of \( \Delta OFV \) was \(<3.84 \) with 1 degree of freedom, then no difference between the two models was discernible and the simpler (reference) model was retained.

### RESULTS

#### Population PK model and parameter estimates

The two-compartment structural model described the concentration-time profiles of entecavir in both HIV- and HBV-coinfected patients and HBV-monoinfected patients. However, due to the fast absorption of entecavir (time to peak concentration, 0.5 to 1.5 h), data collected from patient studies were insufficient to estimate \( K_{a} \). Alternatively, \( K_{a} \) was fixed at 6 h\(^{-1}\) on the basis of a sensitivity analysis. All other parameters were estimated with reasonable 95% confidence intervals (Table 2). According to the parameter estimation, the \( CL/F \) for a typical subject with an NICRC value of 1 was 27.1 liters/h. The estimated typical concentrations of \( V_{2}/F \) and \( Q/F \) were 115 and 1,830 liters, respectively, indicating that entecavir was extensively distributed into tissues. The estimated IIVs for \( CL/F, V_{2}/F, V_{3}/F, Q/F, \) and \( Q/F \) ranged from 30 to 74% (Table 2). In the final model, the additive component of the residual error model was removed because the value was negligible. Model diagnostics suggested that there was no apparent bias in the goodness of fit or the parameter estimation.
0.05), which agreed with the previous findings (entecavir package insert; Pharmaceutical Research and Development, Bristol-Myers Squibb Company). An additional test was performed to evaluate the effect of race on clearance between Asian and non-Asian subjects, with no effect being found.

**Impact of infection status on CL/F.** Evaluation of the effect of infection status on CL/F suggested that the reduction of OFV between models tested with and without the covariate was not statistically significant ($P > 0.05$), and the magnitude of the covariate effect was not clinically relevant. Box plots of Bayesian estimates of individual CL/F values for the two patient populations are shown in Fig. 2.

**Comparability of entecavir PKs in the two patient groups.**

(i) **PK parameters.** Descriptive statistics for Bayesian estimates of the individual CL/F, $V_2/F$, $V_3/F$, and Q/F values in the coinfected and monoinfected patients are provided in Table 3. Comparable parameter estimates were obtained, suggesting that coinfection with HIV and HBV did not affect the PKs of entecavir.

(ii) **Steady-state AUC.** When the dose was normalized to 1.0 mg, comparable individual entecavir AUC values were found in the two patient populations (Fig. 3).

(iii) **GM ratio.** When the dose was normalized to 1.0 mg, the adjusted steady-state GM AUCs were 39.3 and 38.8 ng·h/ml in HIV- and HBV-coinfected and HBV-monoinfected patients, respectively. The adjusted GM ratio was 1.01, and its 90% confidence interval (0.91, 1.12) was within the bioequivalence criterion boundary of 0.80 to 1.25.

**DISCUSSION**

HIV infection causes multidimensional immunosuppression associated with a reduced frequency of spontaneous recovery from HBV infection. HIV induces the impairment of cell-mediated immunity, with the subsequent higher level of replication of hepatotropic viruses (4). In patients infected with HBV, HIV coinfection can lead to decreased rates of anti-HBe and anti-HBs seroconversion and an increase in the level of viral replication, probably through the impairment of the innate and adaptive cellular and humoral immune responses. Therefore, it is recommended that the development of severe immune deficiency (defined as <200 CD4 cells/mm$^3$) be avoided in patients coinfected with HIV and HBV (1). While patients persistently infected with HBV are at risk of development of cirrhosis and hepatocellular carcinoma, patients with HIV and HBV coinfection have an increased risk of progressive liver disease (13). At present, there is no evidence that HBV alters the progression of HIV disease or that HBV alters the response of HIV to HAART (1).

The advent of effective HAART has resulted in HIV-infected patients living longer and, subsequently, greater recognition of the increased risk of death in HIV- and HBV-coinfected patients. Since the symptom-free survival was significantly better in patients with suppressed viral loads (23), the suppression of HBV replication is the main focus of current therapy, which can lead to histological improvement, slow disease progression, and increased long-term survival (20). Among the drugs currently approved for the treatment of HBV (i.e., interferon, peg-interferon, lamivudine, adefovir, telbivudine, and entecavir), entecavir appears to be a viable treatment option for HIV- and HBV-coinfected patients receiving HAART (6, 14). This option was evaluated in study AI463-038. It should be noted that a recent publication identified entecavir as an inhibitor of HIV-1 replication in patients who were not receiving HAART (19). In that report, three HBV- and HIV-coinfected patients experienced a 1-log$_{10}$ drop in their HIV RNA loads. One patient accumulated an HIV-1 variant with lamivudine resistance-conferring mutation M184V after the patient received entecavir monotherapy. This mutation has been shown to confer resistance to entecavir in vitro. As the subjects in study AI463-038 received entecavir in...

**TABLE 2. Population PK parameter estimates of entecavir**

<table>
<thead>
<tr>
<th>Parameter$^a$ (units)</th>
<th>Symbol</th>
<th>Estimate (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_v$ (1/h)</td>
<td>$\theta_1$</td>
<td>6.00 (fixed)</td>
</tr>
<tr>
<td>$\theta_2$ for CL/F (L/h)</td>
<td>$\theta_2$</td>
<td>12.5 (7.78, 17.2)</td>
</tr>
<tr>
<td>$\theta_3$ for CL/F</td>
<td>$\theta_3$</td>
<td>14.6 (9.52, 19.7)</td>
</tr>
<tr>
<td>$V_2/F$ (liters)</td>
<td>$\theta_4$</td>
<td>115 (105, 125)</td>
</tr>
<tr>
<td>$\theta_4$ for Q/F (liters/h)</td>
<td>$\theta_4$</td>
<td>330 (267, 393)</td>
</tr>
<tr>
<td>$\theta_5$ for Q/F</td>
<td>$\theta_5$</td>
<td>$-0.328 (-0.363, -0.293)$</td>
</tr>
<tr>
<td>$V_3/F$ (liters)</td>
<td>$\theta_6$</td>
<td>1,830 (1510, 2150)</td>
</tr>
<tr>
<td>IV (%) for:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Q/F$</td>
<td></td>
<td>30.2 (23.7, 35.5)</td>
</tr>
<tr>
<td>CL/F</td>
<td></td>
<td>46.8 (40.5, 52.3)</td>
</tr>
<tr>
<td>$V_3/F$</td>
<td></td>
<td>39.2 (30.2, 46.5)</td>
</tr>
<tr>
<td>$V_2/F$</td>
<td></td>
<td>74.0 (62.0, 84.3)</td>
</tr>
<tr>
<td>Random residual</td>
<td></td>
<td>41.4 (39.6, 43.0)</td>
</tr>
<tr>
<td>variability (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ The assignment of $\theta$ and the relationship of $\theta$ for each PK parameter are defined in equations 1 to 5.
addition to HAART, the conclusions from that report do not alter the interpretation of the PK assessment of the two populations evaluated in this study.

On the basis of this first evaluation of the entecavir PKs in HIV- and HBV-coinfected patients, it appears that the HIV coinfection has no impact on entecavir exposure, metabolism, or elimination, as discussed below.

It has previously been reported that HIV infection might affect the absorption of antimycobacteral medications in patients with HIV infection or AIDS (22, 24). For instance, the relative bioavailability of rifampin in patients coinfected with HIV and Mycobacterium tuberculosis was 37% lower than that in patients monoinfected patients with M. tuberculosis (11). Although a complete mechanism of action was unclear, HIV infection- and AIDS-related enteropathy and immunodeficiency-associated malabsorption are expected to be contributing factors (21). In contrast, as demonstrated in this study, the steady-state AUC of entecavir in HIV- and HBV-coinfected patients was comparable to that in HBV-monoinfected patients, suggesting that the extent of entecavir absorption was not affected by HIV coinfection.

Since the HIV- and HBV-coinfected patients in study AI463-038 received entecavir in addition to their existing HAART, the impact of HAART on the PKs of entecavir was examined by comparing the entecavir PK parameters (Table 3) and the exposure (Fig. 3) estimated from this study with those from studies in which entecavir was dosed alone. As demonstrated in Table 3, the components of HAART showed no effect on the PKs of entecavir, as comparable entecavir exposures were obtained with and without HAART. Since entecavir is not a substrate, inhibitor, or inducer of cytochrome P450 enzymes (28; entecavir package insert; Pharmaceutical Research and Development, Bristol-Myers Squibb Company), the likelihood of an interaction with the components of HAART, such as protease inhibitors and nonnucleoside reverse transcriptase inhibitor, which are mainly metabolized by cytochrome P450 enzymes in the liver, is low. In addition, the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) components of HAART, lamivudine, tenofovir, and adefovir, which are similar to entecavir and which also undergo phosphorylation to the active form, have not demonstrated a PK interaction with entecavir (5). Evaluation of the interaction was based on measurement of the levels of the unphosphorylated form of entecavir. Entecavir is rapidly phosphorylated to the triphosphate in cells; therefore, the potential that the co-administration of HAART and entecavir may lead to alterations in the triphosphate levels in cells exists. In vitro studies involving combinations of entecavir and HIV nucleoside reverse transcriptase inhibitors have been performed and have shown no antagonistic effects on HBV or HIV, suggesting that a meaningful PK interaction at the triphosphate level is unlikely. The antiviral activities of the HIV NRTIs stavudine, didanosine, abacavir, and zidovudine at up to fivefold the maximum concentration in plasma of each drug were tested in HBV replication assays (9). Since tenofovir and lamivudine also exhibit antiviral activity against HBV, they were tested over a wide range of concentrations in the HBV assays, and their use resulted in no reduction in the anti-HBV activity of entecavir. In assays of the activities of antiviral agents against HIV, when entecavir was added at a concentration up to fourfold the maximum concentration in plasma observed with the 1-mg human dose, entecavir had no effect on the antiviral activity of any of the six NRTIs against HIV. It should be noted that a lack of an in vitro interaction does not rule out an in vivo interaction, although this is highly unlikely on the basis of the results described above.

Entecavir is predominantly eliminated by the kidney, with the urinary recovery of unchanged drug being approximately 70% of the administered dose (entecavir package insert; Pharmaceutical Research and Development, Bristol-Myers Squibb Company). In the current model, the entecavir clearance was expressed as a function of NICRC to quantify the effect of renal function on entecavir exposure. A comparison of entecavir exposure across studies or study populations should be done with caution, and it can be done properly only if the renal functions of the two study populations are comparable. As

### Table 3. Summary of Bayesian estimate of individual PK parameters in HIV- and HBV-coinfected and HBV-monoinfected patients

<table>
<thead>
<tr>
<th>Group</th>
<th>CL/F (liters/h)</th>
<th>V/F (liters)</th>
<th>Q/F (liters/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV- and HBV-coinfected patients (n = 58)</td>
<td>27.9 ± 10.9</td>
<td>117 ± 28</td>
<td>2,142 ± 1,133</td>
</tr>
<tr>
<td>HIV- and HBV-coinfected patients (n = 222)</td>
<td>27.9 ± 10.5</td>
<td>118 ± 33</td>
<td>1,946 ± 789</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviations.

b HIV- and HBV-coinfected patients received entecavir in addition to HAART. HBV-monoinfected patients received entecavir alone.

c Q/F is presented as values obtained at a 1.0-mg dose.

*Fig. 3. Estimated dose-normalized entecavir AUCs in patients with HIV-HBV coinfection and HBV monoinfection. Box plots of estimated individual doses normalized to the AUC in the HIV- and HBV-coinfected and the HBV-monoinfected populations are shown. The black bars inside the boxes mark the median value, and the ends of the boxes are drawn at the first and third quartiles. The top caps are drawn at the largest point that is less than or equal to the third quartile plus 1.5 times the interquartile range. The bottom caps are drawn at the smallest point that is greater than or equal to the first quartile minus 1.5 times the interquartile range. The circles outside of the caps indicate points that fall outside of the range described above.*
presented in Table 1, the renal functions (represented by CL\textsubscript{CR} and NI_CRC) of the HIV- and HBV-coinfected and HBV-monoinfected patients were comparable in this analysis data set; therefore, comparison of the exposures across the two patient populations was justified. The results from this analysis agreed with the previous findings that renal function is the only significant factor affecting entecavir exposure (17).

In addition to the comparable entecavir exposures in the HIV- and HBV-coinfected and the HBV-infected patient groups, it was observed in study AI463-038 that treatment with entecavir at the 1.0-mg daily dose was well tolerated and efficacious at reducing the HBV DNA loads in the HIV- and HBV-coinfected patients, and no new safety issues associated with entecavir treatment were identified, even though the patients had HIV and HBV coinfections and were concomitantly treated with anti-HIV agents (26). At 24 weeks of treatment, patients receiving entecavir in addition to HAART had a 3.66-log\textsubscript{10} drop in their HBV DNA loads, whereas the subjects in the placebo arm had a 0.11-log\textsubscript{10} increase. Moreover, 84% of the patients concomitantly receiving entecavir and HAART had HBV DNA loads of <400 copies/ml, or a ≥2-log\textsubscript{10} reduction in the HBV DNA load from that at the baseline.

In conclusion, the model used in this analysis adequately described the PKs of entecavir in HIV- and HBV-coinfected patients. The PK parameters for the HBV-infected and the HIV- and HBV-coinfected populations were comparable.

ACKNOWLEDGMENT

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REFERENCES