Population Pharmacokinetics of Peramivir in Healthy Volunteers and Influenza Patients

Yumiko Matsuo, Toru Ishibashi, Alan S. Hollister, Toshihiro Wajima

Peramivir is an intravenous anti-influenza agent that inhibits viral growth by selectively inhibiting neuraminidase in human influenza A and B viruses. To characterize its pharmacokinetics, a population pharmacokinetic analysis of peramivir was performed using 3,199 plasma concentration data samples from 332 subjects in six clinical studies in Japan and the United States, including studies with renal impairment subjects, elderly subjects, and influenza patients. A three-compartment model well described the plasma concentration data for peramivir, and creatinine clearance was found to be the most important factor influencing clearance. Age and body weight were also found to be covariates for clearance and the volume of distribution, respectively. No difference in pharmacokinetics was found between genders or between Japanese and U.S. subjects. Small differences in pharmacokinetics were observed between uninfected subjects and influenza patients (clearance was 18% higher and the volume of distribution was 6% lower in influenza patients). Monte Carlo simulations indicated that single adjusted doses of 1/3- and 1/6-fold for patients with moderate and severe renal impairment, respectively, would give areas under the curve comparable to those for patients with normal renal function. The population pharmacokinetic model developed for peramivir should be useful for understanding its pharmacokinetic characteristics and for dose adjustment on the basis of renal function.

Peramivir (S-021812, BCX-1812) is an anti-influenza agent that inhibits viral growth by selectively inhibiting neuraminidase (NA) in influenza A and B viruses (1–4). It exhibits potent inhibitory activity against the NAs of highly pathogenic influenza viruses, such as H5N1 subtypes (5). Peramivir, the first injectable anti-influenza agent, is particularly useful for treating patients who cannot take oral medications, e.g., those requiring mechanical ventilation, those with severe symptoms, or young children. A single intravenous dose of peramivir significantly reduced the duration of influenza symptoms compared with that obtained with the placebo, showed noninferiority to oseltamivir, and was without safety concerns in randomized, controlled, double-blind studies (6, 7). Repeated doses of peramivir also showed efficacy for patients at high risk for complications (8). Consequently, peramivir was approved for use in Japan and South Korea in 2010 and then in the United States in 2014. Peramivir is a useful treatment option for influenza, having the advantages of rapid onset of effect, assured compliance, and no individual variation in absorption.

Peramivir exhibits linear pharmacokinetics (PKs) for doses ranging from 100 to 800 mg, and little accumulation of peramivir in plasma is observed after twice daily or once daily multiple doses (9, 10). After a single infusion, the elimination of peramivir from plasma followed a multieponential decline, with a mean residence time of approximately 3 h and a terminal elimination half-life of approximately 20 h for the slow phase (9, 10). Peramivir is eliminated from plasma predominantly via urinary excretion by glomerular filtration, and more than 80% of the administered drug is excreted unchanged via the urine (9, 10). The usual adult dosage of peramivir approved in Japan is a single dose of 300 mg, administered by intravenous infusion over a period of at least 15 min. For patients at risk of an increased severity of influenza due to comorbidities, once daily repeated doses of 600 mg peramivir are allowed (9). In the United States, the recommended dose for the treatment of acute uncomplicated influenza is a 600-mg infusion for a minimum of 15 min (11). Peramivir is expected to be administered to influenza patients from a wide range of demographic backgrounds, and exposure to peramivir is likely to affect its efficacy and safety. Therefore, the population pharmacokinetic (PPK) characteristics of peramivir should be determined for clinical use.

The aim of this study was to develop a population pharmacokinetic model of peramivir to evaluate the factors that influence its pharmacokinetics. A simulation approach was used to estimate the dose adjustments for significant factors influencing the pharmacokinetics of peramivir.

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MATERIALS AND METHODS

Data for analysis. Pharmacokinetic data and demographic information from six clinical studies in the United States and Japan (6, 9, 10, 12–14) were used for the population pharmacokinetic analyses. Table S1 in the supplemental material summarizes the study designs and dosing regimens of those clinical studies. The clinical studies in the United States consisted of phase 1 studies and included a study with subjects with renal impairment and a study of elderly subjects. The clinical studies in Japan consisted of phase 1 studies with healthy subjects and a phase 2 study with influenza patients. Peramivir was administered by intravenous infusion in all these studies.
clinical studies. All clinical studies were approved by the ethics commit-
tees for each site and conducted in compliance with the Declaration of Helsinki and good clinical practice (GCP).

Peramivir plasma concentrations were determined using a validated
liquid chromatography-tandem mass spectrometry method at Sumika
Chemical Analysis Service, Ltd. (Osaka, Japan), for clinical studies con-
ducted in Japan or BioCryst Pharmaceuticals, Inc. (Birmingham, AL,
USA), for clinical studies conducted in the United States. Peramivir was extracted from plasma by deproteinization and separated by liquid chro-
matography with an XBridge C18 column (Waters Corp., Milford, MA) at
Sumika Chemical Analysis Service, Ltd., or a BetaSIL phenyl column
(Thermo Fisher Scientific Inc., Waltham, MA) at BioCryst Pharmaceutical-
cs, Inc. The column effluent was analyzed using a mass spectrometer (an
Applied Biosystems/MDS Sciex API4000 mass spectrometer [Concord,
Canada] at Sumika Chemical Analysis Service, Ltd., or an Applied Biosys-
tems/MDS Sciex API2000 mass spectrometer [Concord, Canada] at
BioCryst Pharmaceuticals, Inc.) equipped with a turbo ion spray in the
positive ion detection mode. The lower limit of quantification for perami-
vir in plasma was 1.00 ng/ml.

Population pharmacokinetic modeling. Population pharmacoki-
netic analysis was performed using nonlinear mixed effect modeling soft-
ware, NONMEM (version VI; ICONF Development Solutions, Ireland)
(15) with a PREDDPP library and NM-TRAN preprocessor. A first-order
conditional estimation with an interaction (FOCE-I) method was used for
the analysis.

First, a basic population pharmacokinetic model without any covari-
ate (COV; base model) was constructed using the data from phase 1 stud-
ies in the United States (12–14), which included data for healthy young
subjects, elderly subjects, and subjects with renal impairment. The phar-
macokinetics of peramivir were found to follow a three-compartment
model on the basis of evaluation of the structural pharmacokinetic models
with one, two, and three compartments. Total body clearance (CL), inter-
compartmental clearance (Q1, Q2), the volume of distribution of the cen-
tral compartment (V1), and the volumes of distribution of the peripheral
compartments (V2, V3) were defined as the basic pharmacokinetic param-
eters. The interindividuality variability for CL, Q1, Q2, V1, V2, and V3
was assumed to follow a log-normal distribution, and an exponential error
model was used for interindividual variability. A model for intraindi-
viduality variability was selected from an exponential error model, an addi-
tive error model, and a combination error model (the additive error
model plus the exponential error model).

Next, a covariate model was constructed by a forward selection pro-
cedure by using data from the U.S. phase 1 studies (12–14). Age, gender,
body weight (BWT), and creatinine clearance (CLCR) were tested as co-
variates affecting CL, while age, gender, and BWT were tested as covariates
affecting V1. CLCR was estimated on the basis of total body weight by the
Cockcroft-Gault equation (16). A linear model for a continuous variable
(affecting CL), while age, gender, and BWT were tested as covariates
affecting CL, while the volumes of distribution of the peripheral
compartments (V2, V3) were defined as the basic pharmacokinetic param-
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viduality variability was selected from an exponential error model, an addi-
tive error model, and a combination error model (the additive error
model plus the exponential error model).

Next, differences in pharmacokinetics between Japanese and U.S. sub-
jects were examined using data from phase 1 studies in the United States
(12–14) and Japan (9,10) on the basis of the covariate model. Finally, the
differences in pharmacokinetics between uninfected subjects and influ-
enza patients were examined using data from all the studies. The differ-
cences were evaluated by adding these factors to the model as a binary
variable in the population pharmacokinetic analyses. A proportional
model was used for the evaluation of these differences:

\[
PKP = \theta_1 \times (1 + \theta_2 \times COV) \quad \text{(proportional model)}
\]

where COV is a binary variable for the subject group (i.e., 0 for Japanese
subjects and 1 for U.S. subjects or 0 for uninfected subjects and 1 for influ-
enza patients). The fixed model was also selected by use of the OBJ
obtained from NONMEM at a significance level of 5% on the basis of the
likelihood ratio test (final model).

The dose levels in the phase 2 study in Japan (6) were corrected and
used as actual dose levels (266 and 531 mg, corresponding to 300- and
600-mg doses, respectively) for population pharmacokinetic analysis,
since an average of 11.5% of the injection volume was found to be retained
in the venous cannula of the influenza patients on the basis of in vitro
experiments (in-house data) of the intravenous drip infusion.

Model evaluation. The population pharmacokinetic model was eval-
uated by diagnostic plots of the observed plasma concentrations (DV)
versus the mean population predicted plasma concentrations (PRED) and
DV versus individual predicted plasma concentrations (IPRED). In addition,
the nonparametric bootstrap resampling procedure (17) was applied
to assess the stability of the final parameter estimates and to confirm the
robustness of the final model using Wings for NONMEM (N. G. Hololf,
http://wfn.sourceforge.net/). The 1,000 bootstrap sample sets were resam-
pled from the original data set. Next, the parameter estimates for each of
the 1,000 sample sets were estimated using the final model. The medians
and 95% confidence intervals (CIs), obtained as the 25th and 975th small-
est values out of 1,000 parameters estimated from bootstrap sample sets,
were compared with the means and 95% CIs derived from the mean
and its standard error of the final parameter for each parameter estimate.

A visual predictive check (VPC) was performed to evaluate the final
model by comparing the observed plasma concentrations with the 90%predicted intervals (PIs) simulated from the final PPK parameters (18,
19). The 1,000 data sets were simulated from the final PPK parameters
using the original data set as a simulation template. The 90% PIs obtained
from the simulation were superimposed and compared with the observa-
tions. VPC was conducted with stratification for influenza patients and
uninfected subjects with normal renal function (CLCR, 80 to 140 ml/min),
mild renal impairment (CLCR, 50 to 80 ml/min), moderate renal impair-
ment (CLCR, 30 to 50 ml/min), and severe renal impairment (CLCR, 10
to 30 ml/min). The renal function categories were those of the FDA guidance
at the time that the phase 1 renal impairment study of peramivir was
conducted (20).

Model simulation. Monte Carlo simulations were performed with the
final PPK model to evaluate the effects of significant covariates (CLCR and
age) on the area under the plasma concentration-time curve (AUC) for
peramivir. Plasma concentration profiles for 5,000 virtual patients were
simulated to predict the AUC for each category of covariates. Each cova-
riate was simulated from a uniform distribution according to the range of
categories.

To evaluate the effects of renal function (CLCR) and age, CLCR was
divided into four categories: normal renal function (CLCR, 80 to 140 ml/
in), mild renal impairment (CLCR, 50 to 80 ml/min), moderate renal impair-
ment (CLCR, 30 to 50 ml/min), and severe renal impairment (CLCR, 10
to 30 ml/min). Age was simulated for two categories, young
(age, 20 to 60 years) and elderly (age, 60 to 100 years). The other covariate,
BWT, was sampled from normal distributions and had a mean of 62.2 kg
and a standard deviation of 14.0 kg on the basis of the background of the
influenza patients in the phase 2 study in Japan.

To evaluate the effect of dose adjustment on the basis of the renal
function, the AUC for influenza patients with renal impairment was sim-
ulated at the dose set for each category of renal function. Renal function
was divided into the four categories described above, and a uniform distribution was simulated for CLCR in each category. The covariates age and BWT in the final PPK model for the PKs of peramivir were sampled from the distribution was simulated for CLCR in each category. The covariates age and BWT on the basis of the demographics of the patients participating in the phase 2 study in Japan. Corresponding to the 300- or 600-mg dose for patients with normal renal function, the doses were set at 300 or 600 mg (no dose adjustment), 100 or 200 mg, and 50 or 100 mg for patients with mild, moderate, and severe renal impairment, respectively. Simulation was performed for a single intravenous infusion over 15 min at the actual dose calculated.

**RESULTS**

**Population pharmacokinetic analysis.** A total of 3,199 plasma concentrations for 36 healthy subjects in Japan, 98 subjects in the United States (healthy subjects, elderly subjects, and subjects with renal impairment), and 198 influenza patients in Japan from six clinical studies were used for this PPK analysis. The demographics for the analysis population are summarized in Table 1. The numbers of subjects with mild renal impairment (CLCR 50 to 80 ml/min), moderate renal impairment (CLCR 30 to 50 ml/min), and severe renal impairment (CLCR 10 to 30 ml/min) included in this analysis population were 25, 6, and 12, respectively.

Plasma concentrations of peramivir were best described by a three-compartment model, with a combination error model being selected for intraindividual variability. Visual inspections were performed for the relationships between the demographics of the patients and Bayesian-estimated pharmacokinetic parameters (CL, Vf) from the base model. As shown in Fig. S1 in the supplemental material, CL was clearly related to CLCR, while Vf was related to BWT and gender. The model-building process is shown in Table S2 in the supplemental material. In the model-building process, to evaluate covariates, the effect of CLCR on CL was found to be the most significant covariate (model 09, ΔOBJ = −187.152 compared with the base model [model 01]). The effects of BWT (model 11, ΔOBJ = −36.611 compared with model 09) and gender (model 12, ΔOBJ = −4.239 compared with model 11) on Vf and the effect of age on CL (model 13, ΔOBJ = −36.820 compared with model 12) were also found to be significant covariates. The interindividual variability for Qh was excluded from the model because the parameter could not be appropriately estimated (model 14). In addition, the relationship between CL and CLCR was tested under the assumption that CL has an upper limit when CLCR is more than a certain value, because we considered that CL was consistent within the normal range of renal function. The model that assumed an upper limit of CLCR of 115 ml/min for the typical CL best described the relationship between CLCR and CL (full model [model 20], ΔOBJ = −7.930 compared with model 14 and ΔOBJ = −272.752 compared with the base model [model 01]). Next, a backward elimination procedure was performed and the additive effect of gender on Vf was excluded from the model (model 25, ΔOBJ = 4.363 compared with the full model [model 20]). In addition, the intercept for CL was excluded from the model since it was estimated to be close to zero (model 29, ΔOBJ = −0.005 compared with model 25). The interindividual variabilities for CL and Vf were reduced from 96.7% and 18.9%, respectively, in the base model to 27.9% and 14.7%, respectively, in model 29.

The differences in PKs between the U.S. and Japanese subjects

### Table 1 Summary of background data

<table>
<thead>
<tr>
<th>Subject group</th>
<th>Parameter</th>
<th>Age (yr)</th>
<th>Ht (cm)</th>
<th>BWT (kg)</th>
<th>BMI (kg/m²)</th>
<th>SCR (mg/dl)</th>
<th>CLCR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>U.S. subjects</strong></td>
<td>Mean</td>
<td>47</td>
<td>170.7</td>
<td>78.6</td>
<td>26.9</td>
<td>1.7</td>
<td>92.8</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>19</td>
<td>9.9</td>
<td>13.5</td>
<td>3.8</td>
<td>2.1</td>
<td>42.3</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>19</td>
<td>150.0</td>
<td>50.0</td>
<td>18.0</td>
<td>0.6</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>46</td>
<td>172.0</td>
<td>78.6</td>
<td>26.8</td>
<td>1.0</td>
<td>98.5</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>79</td>
<td>189.0</td>
<td>113.0</td>
<td>37.0</td>
<td>10.9</td>
<td>180.6</td>
</tr>
<tr>
<td><strong>Healthy Japanese subjects</strong></td>
<td>Mean</td>
<td>24</td>
<td>172.7</td>
<td>64.4</td>
<td>21.6</td>
<td>0.73</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4</td>
<td>4.8</td>
<td>5.9</td>
<td>1.7</td>
<td>0.10</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>20</td>
<td>163.4</td>
<td>53.3</td>
<td>18.6</td>
<td>0.60</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>23</td>
<td>173.4</td>
<td>64.2</td>
<td>21.4</td>
<td>0.72</td>
<td>141</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>39</td>
<td>182.0</td>
<td>76.8</td>
<td>24.6</td>
<td>0.98</td>
<td>188</td>
</tr>
<tr>
<td><strong>Japanese patients</strong></td>
<td>Mean</td>
<td>34</td>
<td>164.2</td>
<td>62.2</td>
<td>23.0</td>
<td>0.77</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>10</td>
<td>9.1</td>
<td>14.0</td>
<td>4.2</td>
<td>0.18</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>20</td>
<td>143.0</td>
<td>39.2</td>
<td>16.1</td>
<td>0.42</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>32</td>
<td>164.3</td>
<td>60.0</td>
<td>22.3</td>
<td>0.75</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>62</td>
<td>188.5</td>
<td>109.8</td>
<td>44.8</td>
<td>1.25</td>
<td>195</td>
</tr>
<tr>
<td><strong>All subjects</strong></td>
<td>Mean</td>
<td>37</td>
<td>167.0</td>
<td>67.3</td>
<td>24.0</td>
<td>1.03</td>
<td>109.6</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>15</td>
<td>9.6</td>
<td>15.1</td>
<td>4.3</td>
<td>1.23</td>
<td>33.6</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>19</td>
<td>143.0</td>
<td>39.2</td>
<td>16.1</td>
<td>0.42</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>32</td>
<td>167.9</td>
<td>65.1</td>
<td>23.4</td>
<td>0.80</td>
<td>111.3</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>79</td>
<td>189.0</td>
<td>113.0</td>
<td>44.8</td>
<td>10.9</td>
<td>195</td>
</tr>
</tbody>
</table>

*Clinical trials Hi-06-103, Hi-06-104, and Hi-06-105 (BioCryst), which included 57 men (859 samples) and 41 women (690 samples) for a total of 98 subjects (1,549 samples).

*Clinical trials 0712T0611 and 0714T0612 (Shionogi), which included 36 men (1,092 samples) and no women.

*Clinical trial 0722T0621 (Shionogi), which included 101 men (288 samples) and 97 women (270 samples) for a total of 198 subjects (558 samples).

*Data from all clinical trials, which included 194 men (2,239 samples) and 138 women (960 samples) for a total of 332 subjects (3,199 samples).

*Ht, height; BWT, body weight; BMI, body mass index; SCR, serum creatinine; CLCR, creatinine clearance.
were evaluated on the basis of model 29 using phase 1 data from the United States and Japan (model 30). The values of $\theta$ (except for parameters for the difference between the U.S. and Japanese subjects) were fixed at the estimates of model 29, obtained from the data for U.S. subjects, since we intended to evaluate the difference in PKs between the U.S. and Japanese subjects while controlling for differences in BWT, age, and renal function. No difference in CL and $V_i$ was found between the U.S. and Japanese subjects (model 31, $\Delta$OBJ $= -0.008$ for CL compared with model 30; model 32, $\Delta$OBJ $= -0.002$ for $V_i$ compared with model 30). Therefore, the population pharmacokinetic model parameters of the covariate model were reestimated using all the phase 1 data from the U.S. and Japanese uninfected subjects (model 33).

Finally, the differences in PKs between uninfected subjects and influenza patients were evaluated on the basis of the model obtained using all data from the U.S. (phase 1 and phase 2) studies (model 34). The $\theta$ values (except for parameters for the difference between uninfected subjects and patients) were fixed at the estimates of model 33 in uninfected subjects, because we intended to evaluate the differences in pharmacokinetics between uninfected subjects and patients while controlling for differences in BWT, age, and renal function. Differences in both CL and $V_i$ were identified between uninfected subjects and patients (model 35, $\Delta$OBJ $= -119.836$ for CL compared with model 34; model 36, $\Delta$OBJ $= -9.490$ for $V_i$ compared with model 35). The final population pharmacokinetic parameters (all $\theta$ values) were reestimated using the final model including the factor of infection for both CL and $V_i$ and all data (final model [model 37]). CL was estimated to be higher (18%) and $V_i$ was estimated to be lower (6%) in influenza patients than uninfected subjects. The population pharmacokinetic parameters of the final model are shown in Table 2.

### Evaluation of the final population pharmacokinetic model

Diagnostic plots for DV versus PRED and DV versus IPRED demonstrated that the final model adequately described the plasma concentrations, suggesting a good fit of the final model to the data and an absence of bias (Fig. 1). Figure 2 shows the results of VPC, that is, the plots for the observed plasma concentrations and the median and 90% PIs of the plasma concentration profiles simulated from the final model. Plasma concentrations in the phase 1 studies in the United States and Japan were proportionally normalized to those that would be achieved with a 300-mg dose. The median profiles and 90% PIs of the model were consistent with the observed plasma concentration data in all groups.

The stability and robustness of the final PPK model were evaluated using the nonparametric bootstrap procedure. Pharmacokinetic parameters were reestimated with a 79.9% success ratio by the bootstrap method. The median parameter estimates and 95% CIs obtained are shown in Table 2 along with the parameter estimates in the final model. The population parameter estimates obtained from 1,000 bootstrap sample sets were comparable to the estimates from the final models, indicating that the parameter estimates in the final models had little bias and the final model was fairly robust.

### Model simulation

Model simulations were employed to evaluate the effect of covariates (CLCR and age) on the AUC of peramivir at the 600-mg dose on the basis of the final population pharmacokinetic model. The simulation results used to evaluate the

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**TABLE 2 Parameter estimates for the final PPK model with the results of 1,000 bootstrapped runs**

<table>
<thead>
<tr>
<th>Final pharmacokinetic model</th>
<th>Final parameter estimate</th>
<th>Estimate from 1,000 bootstrap sample sets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>For CLCR $&lt; 115$, CL (liters/h) = $(6.67 \times \text{CLCR}/109.6 - 0.212 \times \text{age}/37) \times (1 + 0.176 \times \text{PID})$; for CLCR $\geq 115$, CL (liters/h) = $(6.67 \times 115/109.6 - 0.212 \times \text{age}/37) \times (1 + 0.176 \times \text{PID})$</td>
<td>$6.67$</td>
<td>$6.44$ to $6.90$</td>
</tr>
<tr>
<td>Effect of CLCR on CL</td>
<td>$-0.212$</td>
<td>$-0.291$ to $-0.133$</td>
</tr>
<tr>
<td>Effect of age on CL</td>
<td>$0.176$</td>
<td>$0.134$ to $0.218$</td>
</tr>
<tr>
<td>$V_i$ (liters) = $(1.35 + 8.64 \times \text{BWT}/67.3) \times (1 - 0.0629 \times \text{PID})$</td>
<td>Intercept of $V_i$</td>
<td>$1.35$</td>
</tr>
<tr>
<td>Effect of BWT on $V_i$</td>
<td>$8.64$</td>
<td>$7.44$ to $9.84$</td>
</tr>
<tr>
<td>Effect of infection on $V_i$</td>
<td>$-0.0629$</td>
<td>$-0.116$ to $0.0102$</td>
</tr>
<tr>
<td>$Q_2$ = 5.16 liters/h</td>
<td>$5.16$</td>
<td>$3.94$ to $6.38$</td>
</tr>
<tr>
<td>$Q_3$ = 5.57 liters</td>
<td>$5.57$</td>
<td>$5.15$ to $5.99$</td>
</tr>
<tr>
<td>$Q_4$ = 0.118 liters/h</td>
<td>$0.118$</td>
<td>$0.112$ to $0.124$</td>
</tr>
<tr>
<td>$Q_5$ = 3.29 liters</td>
<td>$3.29$</td>
<td>$3.15$ to $3.43$</td>
</tr>
<tr>
<td>$\omega_{CL}$ (% CV) = 17.8</td>
<td>$17.8$</td>
<td>$13.0$ to $21.6$</td>
</tr>
<tr>
<td>$\omega_{V_1}$ = CV of 16.6%</td>
<td>$16.6$</td>
<td>$11.9$ to $20.3$</td>
</tr>
<tr>
<td>$\omega_{V_2}$ = CV of 14.2%</td>
<td>$14.2$</td>
<td>$10.0$ to $17.4$</td>
</tr>
<tr>
<td>$\omega_{V_3}$ = CV of 15.5%</td>
<td>$15.5$</td>
<td>$10.6$ to $19.1$</td>
</tr>
<tr>
<td>$\omega_{V_4}$ = CV of 18.2%</td>
<td>$18.2$</td>
<td>$14.4$ to $21.2$</td>
</tr>
<tr>
<td>$\omega_{V_5}$ = additive error = CV of 12.6%</td>
<td>$12.6$</td>
<td>$11.4$ to $13.8$</td>
</tr>
<tr>
<td>$\sigma$ for exponential error = 0.489 ng/ml</td>
<td>$0.489$</td>
<td>$--$ to $0.731$</td>
</tr>
</tbody>
</table>

a CI, confidence interval; CLCR, creatinine clearance (in milliliters per minute); BWT, body weight (in kilograms); PID, a flag for influenza patients (0 for uninfected subjects in the phase 1 studies and 1 for influenza patients); $\omega$, inter-individual variability; $\sigma$, intra-individual variability; CV, coefficient of variation; --, not estimated. Age is in years.
The effect of CLCR and age on the PKs of peramivir by renal function are also shown in Fig. 3 and suggest that the AUC was highly dependent on CLCR but minimally influenced by age. The differences in the AUCs between young and elderly patients were about 1.7, 2.8, and 6.3 times higher, respectively, than those for young patients with normal renal function. The simulated AUCs for young patients with mild, moderate, and severe renal impairment, respectively, were 4%, 7%, 13%, and 32% in patients with normal renal function and less than the effect of CLCR.

Next, dose adjustment was simulated on the basis of CLCR so that the adjusted doses for patients with renal impairment would give an AUC comparable to that in patients with normal renal function. Figures 4a and b show the AUC simulated at the adjusted doses on the basis of CLCR corresponding to doses of 600 and 300 mg for patients with normal renal function, respectively. Adjustment of the dosages for patients with moderate and severe renal impairment of 1/3- and 1/6-fold, respectively, would give AUCs comparable to the AUC for patients with normal renal function. The simulated AUC without dose adjustment predicted for patients with mild renal impairment was modestly higher than that predicted for patients with normal renal function.

DISCUSSION
Peramivir, the first neuraminidase inhibitor intended for intravenous administration, has been found to reduce the time needed to alleviate influenza symptoms after a single administration. In this study, we developed a population pharmacokinetic model of peramivir using data from six clinical studies in Japan and the United States including healthy subjects and influenza patients with various backgrounds.

Preliminary population PK analyses were conducted to evaluate the basic PK model on the basis of data from two Japanese phase 1 studies and one Japanese phase 2 study. The results suggested that a three-compartment model better described the PK profiles of peramivir (OBJ = 17,545.856) than a two-compartment model (OBJ = 19,8083.513). Therefore, population PK analyses in this study were started with a three-compartment model as a basic PK model. This is because a two-compartment model did not adequately capture the wide range of peramivir concentrations, as the lower limit of quantification of peramivir was 1 ng/ml, which was set to measure concentrations at the 50% inhibitory concentration (IC50) range of peramivir (median IC50 range for the A/H1N1 subtype, 1.15 to 21.59 nM [0.44 to 8.26 ng/ml]) (6, 7) and was markedly lower than the maximum concentration in plasma (Cmax; geometric mean Cmax after a single 800-mg dose in a phase 1 high-dose study in Japan, 85,200 ng/ml).

CLCR and age were found to be significant covariates for CL and BWT on Vf. No difference in pharmacokinetics was observed by gender. CL was calculated to be reduced by 0.87 to 0.91% for every 10-year increase in age in the range of 20 to 80 years and to be reduced by 9.4 to 60.5% for every 10-ml/min decrease in CLCR in the range of 10 to 110 ml/min. Vf was calculated to be increased by 12.4 to 24.7% for every 10-kg increase in body weight in the range of 30 to 80 kg. CLCR was found to be the most important factor influencing the pharmacokinetics of peramivir, which is consistent with the fact that peramivir is mainly excreted unchanged in urine (9). The final population pharmacokinetic model, in which CL was shown to be linearly related to CLCR in the range of CLCR values below 115 ml/min but was independent of CLCR in the range of CLCR values over 115 ml/min, best described the relationship between the CL of peramivir and CLCR. As peramivir is predominantly eliminated by glomerular filtration, peramivir CL is considered to be proportional to CLCR especially at the lower range of CLCR values (e.g., <100 ml/min). On the other hand, at the high range of CLCR values, CLCR may not be accurately estimated and peramivir CL could not be assumed to be proportional to CLCR. Therefore, with consideration for visual inspection of the relationship between CL and CLCR (see Fig. S1 in the supplemental material), we adopted the model with a CLCR threshold for the relationship with CL. On the basis of the population mean of the final model, the CL of peramivir in a healthy subject (age, 37 years) is 113 ml/min.

No differences in pharmacokinetics between the U.S. and Japanese subjects were found after incorporation of covariates (CLCR, BWT, and age) into the population model. Differences in pharmacokinetics between uninstructed subjects and influenza patients were suggested in the population pharmacokinetic analysis, and CL was estimated to be 18% higher and Vf was estimated to be 6% lower in patients. Although the reason for these differences re-
mains unknown, the differences are not considered clinically significant on the basis of the accumulated safety and efficacy data from clinical studies and toxicological data from preclinical studies (6–10, 12, 13). Possible reasons are differences in pharmacokinetic blood sampling schedules and administration methods between the phase 1 studies and the phase 2 study. In the phase 1 studies, infusion pumps were used and intensive pharmacokinetic sampling was performed, while in the phase 2 study, peramivir was administered by intravenous drip infusion and sparse pharmacokinetic samplings were performed (2 to 4 sampling points per patient for most patients and 9 sampling points for three patients). As described in the Materials and Methods section, the dose levels in the phase 2 study in Japan were corrected because 11.5% of the injection volume was retained in the venous cannula.
of the intravenous drip infusion. Although the correction is not considered to significantly affect the model development, it would be one of the limitations when interpreting the results. Another possible explanation for the differences is that increased cardiac output in influenza patients would increase renal blood flow, which results in increased renal clearance.

The PPK model does not appear to fit well at high concentrations (Fig. 1). Those concentrations were around the \( C_{\text{max}} \) at the 800-mg dose and were tested only in the Japanese phase 1 study. In addition, a less than optimal fit was observed in the lower range of plasma concentrations at more than 96 h postdose in Fig. 2d to f. This is probably because of the wide range of plasma concentrations, which could not be adequately described even by a three-compartment model. However, the diagnostic plots suggested that the model described the overall plasma concentrations and could be considered sufficient for AUC simulations.

According to the results of population PK modeling and simulation, AUC was highly dependent on \( \text{CL}_{\text{CR}} \) and minimally influenced by age. Dose adjustment for patients with renal impairment on the basis of \( \text{CL}_{\text{CR}} \) was examined using an exposure index of AUC since the AUC was suggested to be the best descriptor for the efficacy of peramivir in animal studies (10). The AUC of peramivir is highly dependent on \( \text{CL}_{\text{CR}} \) and the effect of age on AUC is considered to be negligible in comparison.

The results of simulation demonstrated that the adjustment of the dosages for patients with moderate and severe renal impairment by 1/3- and 1/6-fold, respectively, would give AUCs comparable to those in patients with normal renal function. For patients with mild renal function, no dose adjustment is proposed in this paper, in consideration of the clinical benefits and the safety experience in this exposure range. Thus, no dose adjustment for patients with mild renal function impairment is proposed for peramivir in clinical situations, because many patients have mild renal impairment and renal impairment may not be recognized in some of them. The simulated AUCs in patients with mild renal impairment without dose adjustment were modestly higher than those in patients with normal renal function. However, the simulated AUCs obtained with a 600-mg dose in patients with mild renal impairment (median AUC, 121,036 ng \( \cdot \) h/ml) would not exceed those observed with 800-mg once daily dosing in the Japanese phase 1 study (geometric mean of the daily AUC, 130,876 ng \( \cdot \) h/ml) (10), in which multiple doses of peramivir given over 6 days were well tolerated. The simulated \( C_{\text{max}} \) at the adjusted dose in patients with renal impairment did not exceed that in subjects with normal renal function, because \( C_{\text{max}} \) was not affected by renal function (\( \text{CL}_{\text{CR}} \)), suggesting that there should be no safety concern with respect to dose adjustment. The effect of hemodialysis on peramivir PKs was evaluated in a previous study with sub-
jects with end-stage renal disease requiring hemodialysis after a single intravenous dose of peramivir at 2 mg/kg of body weight prior to or immediately following a 4-hour hemodialysis (14). Peramivir was removed by hemodialysis, with a 4-hour hemodi-
alysis reducing the peramivir systemic exposure by 73% to 81%.

The significance criteria of 0.05 for forward selection and 0.01 for backward elimination were adopted in this analysis so that as many covariates as possible could be incorporated into the model, which was being planned for use in simulations investigating the magnitude of covariate effects on peramivir PKs. The simulation results indicated that the AUC of peramivir is highly dependent on CLCR and the effects of age, body weight, and differences between uninfected subjects and influenza patients on AUC are considered to be negligible in comparison, suggesting that the model could be simplified by removing covariates which have small effects on PKs (age on CL, effect of infection on CL, and BWT on V1).

The simplified model is presented in Table S3 in the supple-
mental material.

In conclusion, the population pharmacokinetic model for peramivir was developed using plasma concentration data from six clinical studies in Japan and the United States, and CLCR was found to be the most important factor influencing the pharmacoki-
netics of peramivir. Age and BWT were also covariates on CL and V1, respectively. Dose adjustment based on renal function (no dose adjustment for patients with a CLCR of >50 ml/min, a 1/3-fold dose adjustment for patients with a CLCR of 30 to 50 ml/min, and a 1/6-fold dose adjustment for patients with a CLCR of 10 to 30 ml/min) is suggested to provide AUCs comparable to those in patients with normal renal function. This dose adjustment informa-
tion should contribute to the proper clinical use of peramivir for patients with renal impairment.

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