Characterisation of exposure versus response of edoxaban in patients undergoing total hip replacement surgery

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Summary
Edoxaban is an oral direct factor Xa inhibitor approved for the prevention of venous thromboembolism (VTE) in Japan. The objectives of this analysis were to characterise the population pharmacokinetics (PK) of edoxaban and the relationships between edoxaban exposure and clinical outcomes in a phase IIb study of surgical patients following total hip replacement (THR). A total of 1,795 subjects from a phase IIb study, 10 phase I studies, and three phase Ila studies were included in the PK analysis. The exposure-response analysis included data from surgical patients assigned to edoxaban in the phase IIb study. Edoxaban disposition in healthy and post-surgical patients was well-described with a linear, two-compartment model. Creatinine clearance was significantly correlated with edoxaban clearance and the rate of oral absorption was affected by surgery. The probability of a post-operative VTE was significantly correlated with steady-state metrics of edoxaban exposure estimated for each subject by Bayesian post-hoc methods with age and gender being the significant and expected covariates. The incidence of bleeding was low in these studies and hence no exposure-response relationship could be identified. These analyses suggest that edoxaban has a predictable anticoagulant effect in this patient population leading to dose-proportional reduction in incidence of VTE with low incidence of bleeding.

Keywords
Edoxaban, factor Xa inhibitor, population pharmacokinetics, venous thromboembolism

Introduction
Several novel anticoagulants that inhibit either thrombin (factor II) or factor (F) Xa are being developed (1). FXa is located at the confluence of the intrinsic and extrinsic coagulation pathways. FXa binds to FVa, which along with calcium and the phospholipid surface of the platelets and other cells, forms the prothrombinase complex. This complex activates the formation of thrombin from prothrombin and is the primary site of amplification in the coagulation cascade. Direct FXa inhibitors bind to both free FXa and FXa within the prothrombinase complex, and therefore decrease thrombin generation (2). Edoxaban is an oral direct FXa inhibitor being developed for the prevention and treatment of thromboembolism and has been approved in Japan for the prevention of venous thromboembolism (VTE) in patients following hip and knee replacement surgery (3–7).

Edoxaban selectively and competitively inhibits both free and prothrombinase-bound FXa with observed Ki values of 0.561 and 2.98 nM, respectively, for human FXa (8). In human plasma, edoxaban doubled prothrombin time and activated partial thromboplastin time at concentrations of 0.256 and 0.508 μM, respectively (8). Edoxaban is rapidly absorbed, reaching a maximum concentration (Cmax) 1 to 2 hours (h) after administration with a mean terminal elimination plasma half-life (t1/2) of 8 to 10 h in healthy volunteers (9). The disposition of edoxaban is characterised by linear pharmacokinetics (PK) with exposure increasing proportionally to a range of doses from 10 to 150 mg, providing a predictable and consistent exposure within subjects (9). Edoxaban is eliminated through multiple pathways, with approximately 50% of systemically absorbed drug eliminated via renal excretion (9,10). Additional phase 1 studies demonstrate that edoxaban has limited potential to prolong QTc (11), increased exposure with strong p-glycoprotein inhibitors (12, 13), and subjects could be safely switched from warfarin (at least 24 h after the last dose) (14) or enoxaparin 1 mg/kg (12 h post-last dose) (15).

Deep-vein thrombosis (DVT) and pulmonary embolism (PE) are common after total hip replacement (THR) surgery unless effective thromboprophylaxis is given. Edoxaban demonstrated a significant (p<0.001) dose response relationship over the dose range 15 to 90 mg once daily, and edoxaban-treated subjects had a

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significantly lower incidence of VTE compared with those treated with dalteparin in patients undergoing THR (16).

The purpose of this analysis was to use pharmacometric analyses to identify possible extrinsic or intrinsic factors that may significantly impact efficacy and safety of edoxaban following hip replacement surgery.

Materials and methods

Study description

A population PK model was built as the first step in the exposure versus response and PK analysis. Population PK model development was based on data from 10 phase I studies (including single ascending and multiple ascending dose, biopharmaceutic, and drug-drug interaction studies), two PK/pharmacodynamic (PD) studies in patients with atrial fibrillation (AF), and one phase IIa study for the prevention of VTE in patients undergoing elective hip replacement, in addition to data from the phase IIb study (NCT00398216; see Suppl. Material 1.1 for baseline demographics of the PK analysis set, available online at www.thrombosis-online.com). The phase I studies were primarily intensively sampled and were included to inform PK model building for edoxaban. Table 1 summarises the designs of the studies included in these analyses.

Phase IIb study for PD and efficacy analysis

This was a multicentre, multinational, randomised, parallel group, double-blind, double-dummy phase IIb study of the efficacy and safety of multiple doses of oral edoxaban compared with dalteparin for the prevention of VTE in adult patients following unilateral THR. The details of this study have been published previously (16). Briefly, patients were randomised to edoxaban 15, 30, 60, or 90 mg once daily or subcutaneous dalteparin once daily (initial dose 2,500 IU, subsequent doses 5,000 IU). Study drug was commenced 6 to 8 h after hip replacement surgery (day 1) and continued for a period of 7 to 10 days (end of treatment). Seven plasma samples were collected for PK and PD analysis during three study visits: screening, day 1, and end of treatment. The primary outcome measure of efficacy was the incidence of total VTE during the 7 to 10 days after the initial dose of study drug (first dose through the end of treatment visit). Total VTE was defined as the composite of DVT detected by venography (both proximal and distal) and symptomatic DVT or PE documented by objective testing. The primary safety outcome measure was the incidence of the composite of major and clinically relevant non-major (CRNM) bleeding during the 10 days after the first dose of study drug. The secondary outcome measure of safety was the incidence of any bleeding, defined as the composite of major, CRNM, and minor bleeding during this same time period.

Bioanalytical methods

An analytical method was developed and validated by Quotient (formerly Biodynamics), Rushden, Northamptonshire, UK, to quantitate edoxaban in lithium heparin human plasma samples. Edoxaban-D6 was used as the internal standard (IS). Plasma samples (0.2 ml) were prepared using a liquid-liquid extraction procedure to isolate the analyte and IS from human plasma. Following reconstitution, sample extracts were analysed by turbo ion spray, liquid chromatography/tandem mass spectrometry (LC/MS/MS) in the positive ionisation mode. The assay had a demonstrated lower limit of quantitation (LLOQ) of 1 ng/ml for edoxaban while the upper limit of the assay range was 500 ng/ml. Precision of quality control (QC) samples prepared at 1, 3, 125, and 375 ng/ml was ≤10.1% for intra-assay % coefficient of variation (CV) and ≤12.5% for inter-assay %CV. Accuracy of QC samples prepared at 1, 3, 125, and 375 ng/ml ranged from –16.0% to 6.8% for intra-assay precision (% relative standard error [RSE]) and from –6.4% to 1.5% for inter-assay precision. Dilution QCs were prepared at a concentration of 1,250 ng/ml, and a dilution factor of 10 showed intra-assay accuracy (%CV) and precision (%RSE) to be 2.5% and 1.4%, respectively, as part of the assay validation.

Population PK model development

The data set for population PK analysis included 1,795 subjects, of which 713 (282 males, 431 females) underwent hip replacement surgery in the phase IIb study. Observations below the LLOQ (5% of observations) were considered to be missing. Only subjects randomised to receive edoxaban in the phase IIb study were included in the exposure-response analysis data set.

Initially, exploratory graphical and regression analyses were performed using TIBCO Spotfire S+ 8 (TIBCO Software Inc., Seattle, WA, USA). Subsequently, candidate models were fit to the data and the best model was selected based on goodness-of-fit plots. Inter-subject variability terms and the residual error model were evaluated during the model development process. Population PK models were developed using the non-linear mixed effects modelling (NONMEM) program (version 6, ICON Development Solutions, Baltimore, MD, USA).

Covariates

In the population PK analysis, age, gender, race, health status (volunteer, AF patient, or surgical patient), and body size metrics (including body weight and body mass index [BMI]) were evaluated as covariates on apparent volume of the central compartment (Vc/F) and apparent clearance (CL/F); additionally, baseline creatinine clearance (CLcr) and hepatic function tests, including alanine aminotransferase, aspartate aminotransferase, and total bilirubin, were evaluated as covariates on CL/F. Surgery, formulation,
dose administration with food, and concomitant administration of a proton pump inhibitor (esomeprazole) were tested as covariates on absorption parameters, including the absorption lag time, absorption rate constant (Ka), and relative oral bioavailability. Concomitant esomeprazole was also evaluated as a covariate on CL/F and Vc/F. CL\(_{\text{CR}}\) was computed by using the Cockcroft-Gault equation (17).

### Covariate models

Continuous covariates (centered about standard values) were included in the model as follows:

\[
\theta_i = \theta_{\tau} \cdot \left( \frac{Cov}{Cov_{\text{med}}} \right)^{K_{\text{cov}}}
\]

where \(\theta_i\) and \(\theta_{\tau}\) are the parameter estimate and the value of the covariate, respectively, for subject, \(i\), \(Cov_{\text{med}}\) is the median value of the covariate, and \(K_{\text{cov}}\) represents the influence of the covariate on the typical value of the parameter in the population, \(\theta_{\tau}\).

Categorical covariates were introduced in the model as follows:

\[
\theta_i = \theta_{\tau} \cdot e^{(Cov_{i}/K_{\text{cov}})}
\]

where \(Cov_{i}\) is a binary variable.

Covariate screening was performed using stepwise addition at \(p<0.01\) for all covariates. To refine the model, stepwise addition was followed by a stepwise deletion process (\(p<0.01\)) wherein the least important (as judged by change in –2*log-likelihood) covariates were deleted in a stepwise fashion until only significant covariates remained. Covariates that were not clinically significant, defined as covariates demonstrating less than 20% effect on PK parameters or negligible explanatory impact on the relevant inter-subject omega \((\omega^2)\) term (<5%), were removed from the model (18).

Model development was guided by examination of diagnostic plots to assess the goodness-of-fit of models to the data. The first-order method in NONMEM was used for population PK model-building to reduce run times after evaluation of key models showed consistent results using first order conditional estimation. First-order conditional estimation method with interaction was used for estimation of key models, model refinement and final parameter estimation. Standard errors for PK parameter estimates

### Table 1: Summary of clinical studies and edoxaban treatments included in the population PK analysis.

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Population</th>
<th>Study type</th>
<th>N*</th>
<th>Edoxaban treatments</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (16)</td>
<td>Caucasian following hip replacement</td>
<td>IIb</td>
<td>713</td>
<td>15, 30, 60, 90 mg od</td>
<td>7 to 10 d</td>
</tr>
<tr>
<td>2†</td>
<td>Caucasian following hip replacement</td>
<td>Ila</td>
<td>603</td>
<td>15, 30, 60 mg bid 30, 60, 120 mg od</td>
<td>7 to 10 d</td>
</tr>
<tr>
<td>3 (33)</td>
<td>Japanese with NVAF</td>
<td>Ila</td>
<td>23</td>
<td>5 mg od x 2 weeks, then 15 mg od x 2 weeks, then 30 mg od x 2 weeks</td>
<td>6 weeks</td>
</tr>
<tr>
<td>4 (33)</td>
<td>Japanese with NVAF</td>
<td>Ila</td>
<td>32</td>
<td>30 mg bid x 2 weeks, then 45 mg bid x 4 weeks, then 60 mg bid x 4 weeks</td>
<td>10 weeks</td>
</tr>
<tr>
<td>5 (9)</td>
<td>Healthy Caucasian males</td>
<td>I</td>
<td>95</td>
<td>10, 30, 60, 90, 120, 150 mg od fasted; 60 mg bid, 90 mg od, 120 mg od with food, 60 mg od fasted and fed</td>
<td>SAD: SD MAD: 10 d</td>
</tr>
<tr>
<td>6†</td>
<td>Healthy Caucasian and Japanese males</td>
<td>I</td>
<td>72</td>
<td>30, 60, 90, 120, 150 mg fasted; 60 mg fasted and fed</td>
<td>SD</td>
</tr>
<tr>
<td>7 (34)</td>
<td>Healthy Caucasian elderly males and post-menopausal females</td>
<td>I</td>
<td>18</td>
<td>90 mg od with food</td>
<td>10 d</td>
</tr>
<tr>
<td>8 (35)</td>
<td>Healthy Caucasian males</td>
<td>I</td>
<td>60</td>
<td>30, 60, 120 mg</td>
<td>SD</td>
</tr>
<tr>
<td>9†</td>
<td>Healthy Caucasian males</td>
<td>I</td>
<td>8</td>
<td>60 mg: tablet vs. powder via Enterion capsule, vs. liquid via Enterion capsule</td>
<td>SD x 4</td>
</tr>
<tr>
<td>10 (36)</td>
<td>Healthy Caucasian and Japanese males</td>
<td>I</td>
<td>32</td>
<td>60 mg with and without food</td>
<td>SD x 2</td>
</tr>
<tr>
<td>11 (37)</td>
<td>Healthy Caucasian elderly males</td>
<td>I</td>
<td>10</td>
<td>60 mg bid with food</td>
<td>7 doses</td>
</tr>
<tr>
<td>12 (38)</td>
<td>Healthy Caucasian</td>
<td>I</td>
<td>32</td>
<td>60 mg oral tablet vs. oral solution, with and without esomeprazole 20 mg od x 4</td>
<td>SD x 2</td>
</tr>
<tr>
<td>13 (39)</td>
<td>Healthy Caucasian</td>
<td>I</td>
<td>54</td>
<td>60 mg od with and without aspirin 325 mg</td>
<td>5 doses</td>
</tr>
<tr>
<td>14 (14)</td>
<td>Healthy Caucasian</td>
<td>I</td>
<td>43</td>
<td>60 mg od vs. matching placebo 24 hours post warfarin treatment (INR 2.0 to 3.0)</td>
<td>5 doses</td>
</tr>
</tbody>
</table>

*Number of subjects in population PK analysis; †unpublished studies, Daiichi Sankyo. NVAF, non-valvular atrial fibrillation; bid, twice daily; MAD, multiple ascending dose; od, once daily; SAD, single ascending dose; SD, single dose.

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were obtained by bootstrap resampling (100 replicates) of the PK data set (19).

Exposure–clinical endpoint relationships

Exposure–response model development included only data from the phase Ib study. Individual metrics of exposure, including the steady-state area under the curve from 0 to 24 h (AUCss), steady-state peak (Cmax,ss), and trough (Cmin,ss) plasma concentrations of edoxaban were calculated from the individual post-hoc Bayesian predictions obtained from the population PK model and individual data. Imputation for 11 patients (1.5%) with no PK data was at the median covariate-adjusted exposure. For these subjects, individual PK parameters were computed for each subject based on the final population PK model and the relevant characteristics of each subject (i.e. CLcr). These parameters were then used in lieu of post-hoc Bayesian estimated parameters to calculate individual metrics of exposure for subjects lacking PK data. Relationships between individual edoxaban exposures and incidence of VTE, major bleeding, and major and CRNM bleeding were examined using linear logistic regression models to determine which metric provided the best statistical fit for each of the endpoints. The binary event of whether the patient experienced a clinical response of interest was considered. Goodness of fit of the model was evaluated using diagnostic plots.

Each measure of edoxaban exposure, BMI or weight, age, gender, and geographic region (North America and Western Europe, Japan, or Eastern Europe) was evaluated as a covariate using stepwise addition or deletion of model terms to identify predictors of the primary and secondary clinical responses of interest. For each clinical endpoint, a model of the following form was evaluated:

clinical endpoint ~ edoxaban exposure + covariates + 2-way interactions

The statistical significance of each covariate was examined and the model fit was evaluated using Akaike’s information criterion and diagnostic plots. Analysis of covariates for the incidence of bleeding events (major and major plus CRNM) and incidence of VTE were performed using S+ version 8.

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Estimate</th>
<th>RSE (%)*</th>
<th>Estimated variability (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (l/h)</td>
<td>32.3</td>
<td>1.2</td>
<td>–</td>
</tr>
<tr>
<td>Vc/F (l)</td>
<td>243</td>
<td>2.2</td>
<td>–</td>
</tr>
<tr>
<td>Q/F (l/h)</td>
<td>5.86</td>
<td>3.1</td>
<td>–</td>
</tr>
<tr>
<td>Vp/F (l)</td>
<td>116</td>
<td>10.0</td>
<td>–</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>7.21</td>
<td>47.9</td>
<td>–</td>
</tr>
<tr>
<td>Ts (h)</td>
<td>0.425</td>
<td>2.5</td>
<td>–</td>
</tr>
<tr>
<td>KCL/F-CLcr</td>
<td>0.350</td>
<td>8.0</td>
<td>–</td>
</tr>
<tr>
<td>KKa-Food</td>
<td>–1.14</td>
<td>32.5</td>
<td>–</td>
</tr>
<tr>
<td>KKa-Surgery 12 hours prior</td>
<td>–1.53</td>
<td>23.4</td>
<td>–</td>
</tr>
<tr>
<td>KKa-Surgery 6 hours prior</td>
<td>–3.76</td>
<td>5.9</td>
<td>–</td>
</tr>
<tr>
<td>ωCL/F²</td>
<td>0.041</td>
<td>12.0</td>
<td>20.2</td>
</tr>
<tr>
<td>ωVc/F²</td>
<td>0.122</td>
<td>8.3</td>
<td>34.9</td>
</tr>
<tr>
<td>ωVp/F²</td>
<td>0.723</td>
<td>28.4</td>
<td>85.0</td>
</tr>
<tr>
<td>ωKa²</td>
<td>2.787</td>
<td>10.4</td>
<td>166.9</td>
</tr>
<tr>
<td>ωTlag²</td>
<td>0.018</td>
<td>8.3</td>
<td>13.2</td>
</tr>
<tr>
<td>σ² phase I</td>
<td>0.113</td>
<td>11.0</td>
<td>33.6</td>
</tr>
<tr>
<td>σ² phase II</td>
<td>0.661</td>
<td>6.0</td>
<td>81.3</td>
</tr>
<tr>
<td>σ² phase Ib, Hip Study</td>
<td>0.974</td>
<td>5.2</td>
<td>98.7</td>
</tr>
</tbody>
</table>

* RSE, absolute value of SE / Estimate × 100%; † Intersubject variability = \( \sqrt{\sigma^2} \), residual variability = \( \sqrt{\sigma^2 + \epsilon^2} \), –, not applicable. See text for parameter definitions.

Results

Population PK model

A two-compartment model with first-order absorption, a lag time, and first-order elimination was used to fit the PK data set. Inter-subject variability on PK parameters and residual error was assumed to follow a log normal distribution. Eta (\( \eta \)) shrinkage was reasonable, ranging from 29% to 45% for Ka, CL/F, and Vc/F, and estimated to be 68% and 75% for the apparent volumes of the peripheral compartments (Vp/F) and absorption lag time (Tlag), respectively. Epsilon (\( \epsilon \)) shrinkage was <12%.

The stepwise addition of covariates resulted in a full model including statistically significant (p<0.01) effects of CLcr, hip replacement surgery, gender, body weight, food, and formulation. After removing clinically irrelevant effects, the model included an effect of CLcr on CL/F and effects of surgery and food on Ka (see Suppl. Material 1.2 for graphical displays of the impact of covariates on edoxaban exposure, available online at www.thrombosis-online.com).
The final population PK model is described by the following equations:

\[
\frac{CL/F_i}{CL/F_T} = \left( \frac{CL_{CR}}{CL/F_T} \right)^{K_{CL/CR}} \cdot e^{\eta_{CL/F_T}},
\]

\[
\frac{Vc/F_i}{Vc/F_T} = e^{\eta_{Vc/F_T}},
\]

\[
\frac{Q/F_i}{Q/F_T} = \left( \frac{Vp/F_i}{Vp/F_T} \right)^{K_{Q/Vp}} \cdot e^{\eta_{Q/Vp}},
\]

\[
K_a = K_a \cdot e^{(K_{K_a/FOOD} + K_{K_a/SURGERY12h} + K_{K_a/SURGERY6h}) \cdot \eta_{K_a}},
\]

\[
T_{lag_i} = T_{lag_T} \cdot e^{\eta_{T_{lag}}},
\]

where subscript \(i\) represents the parameter estimate for subject \(i\) and subscript \(T\) represents the typical value of the parameter estimate for the population for \(CL/F, Vc/F,\) the apparent intercompartment clearance \((Q/F), Vp/F, K_a,\) and \(T_{lag} \cdot \frac{CL_{CR}}{CL/F_T}.\)

\(K_{CL/CR}, K_{K_a/FOOD}, K_{K_a/SURGERY12h} \) and \(K_{K_a/SURGERY6h}\) represent the effect of the respective covariate on the typical parameter estimate, and \(\eta_i\) represents inter-subject variability for respective PK parameters, where \(\eta_i\) were normally distributed with mean of zero and variance \(\omega^2.\) A log normal error model was used to describe residual variability specified as \(\log(Y_{ij}) = \log(Y_{Pi}) + \epsilon_{ij,\text{PhaseI}} + \epsilon_{ij,\text{PhaseIIa}} + \epsilon_{ij,\text{PhaseIIb,Hip Study}}\)

where \(Y_{ij}\) and \(Y_{Pi}\) were the observed and predicted concentration for subject \(i\) at timepoint \(j\) and \(\epsilon_{ij}\) were normally distributed with mean of zero and variance \(\sigma^2.\) The magnitude of residual variability for the phase IIa and phase IIb studies was larger than that for the phase I studies in healthy subjects and were estimated in the final model (see Suppl. Material 1.3, available online at www.thrombosis-online.com). Parameter estimates are presented in Table 2.

\(CL_{CR}\) was a significant \((p<0.001)\) predictor of apparent edoxaban clearance. Inclusion of \(CL_{CR}\) as a covariate on apparent edoxaban clearance reduced the variance of inter-subject variability \((\omega^2)\) CL/F by 24%. Absorption of edoxaban was rapid in healthy volunteers after a median lag period of 26 minutes. Surgery significantly \((p<0.001)\) slowed the rate of edoxaban absorption. The

![Figure 1: Diagnostic plots for final model. Observed vs. population predicted (upper left panel) and individual predicted (upper right panel) plasma concentrations of edoxaban (log domain). Population residual error vs. time since the first dose (lower left panel) and population predicted concentration (lower right panel). Predicted concentrations are the post-hoc predictions from NONMEM. Solid line is unity; blue line represents a smoothing function.](image-url)
typical first-order $K_a$ was estimated to be $7.17 \text{ h}^{-1}$ in healthy subjects, 1.68 $\text{ h}^{-1}$ when dosed 12 to 24 h post-operatively, and 0.17 $\text{ h}^{-1}$ when dosed 6 to 8 h post-operatively. $K_a$ was associated with large inter-subject variability of 168%.

The final population PK model adequately described the data. Figure 1 shows that residual errors were approximately normally distributed over time and predicted concentrations. The predicted concentrations match the observed concentrations satisfactorily, with substantial scatter around the line of unity due to noise in the surgical population (see Suppl. Material 1.3, available online at www.thrombosis-online.com). There was a general lack of correlation among inter-subject variabilities for each parameter ($\eta$'s), and the $\eta$'s were symmetrically distributed and generally unbiased (see Suppl. Material 1.3, available online at www.thrombosis-online.com).

### Exposure–clinical endpoint relationships

#### VTE model

A linear logistic regression model described the significant relationship between the declining incidence of VTE and increasing edoxaban exposure (Table 3; see also Suppl. Material 1.4 for a table of clinical outcomes by treatment arm, available online at www.thrombosis-online.com). Each of the exposure metrics was reasonably predictive of the incidence of VTE based on visual inspection of the observed VTE rates and predicted values (Fig. 2) and the statistical significance ($p<0.001$) of the inclusion of these three exposure metrics as factors in the regression models (Table 3). In addition to edoxaban exposure, age, gender, and geographic region significantly influenced the incidence of VTE (Table 3). A higher incidence of VTE was observed at Eastern European study sites compared with those in North America/Western Europe. Increasing age was associated with an increased incidence of VTE despite higher mean exposure of edoxaban in the elderly due to decreased apparent edoxaban clearance with age. Post-hoc apparent clearance of edoxaban (mean [%CV]) was calculated to be 30.9 l/h (33%) in elderly patients (age ≥65 years) vs. 36.3 l/h (34%) in younger patients. When examined by gender, the decrease in the incidence of VTE with increasing edoxaban exposure in female subjects was significant, while in male subjects the decrease was not significant.

#### Bleed models

There was a low incidence of bleeding events (range: 2.6% to 5.4% for any bleeding event) across edoxaban treatment arms over the 10-day period following THR. Hence, there were no significant relationships between metrics of edoxaban exposure at steady state and incidences of major bleeding or major plus CRNM bleeding events detected by logistic regression analysis.

### Discussion

The disposition of edoxaban was well-described by a linear, two-compartment model with first-order absorption. CLCR and administration of doses with food or following surgery were the only covariates identified as having statistically significant, clinically relevant influences on edoxaban PK. Edoxaban absorption in postsurgical patients was characterised by a slower absorption rate probably caused by decreased gastric motility following major surgery (20). These findings are plausible given the known disposition kinetics and pharmacology of edoxaban. However, it is noted that the final population PK model still has large residual variability, and the abovementioned findings will be further evaluated as more data become available.

A clear exposure versus VTE response relationship was identified for edoxaban using logistic regression analysis. In addition, oral edoxaban was superior ($p<0.005$) to the comparator group receiving dalteparin (5,000 IU once daily), for which the incidence of VTE was 43.8% (16). The plasma concentration of edoxaban, as either $AUC_{\text{ss}}$, $C_{\text{min,ss}}$, or $C_{\text{max,ss}}$, was a significant predictor of VTE in these patients. These three measures of plasma exposure were all similarly predictive with same order of magnitude of statistical significance ($p<0.005$).

No relationship was identified between edoxaban exposure metrics and bleeding incidence following 10 days of treatment. The lack of correlation between edoxaban exposure and bleeding
incidence is in part related to the low incidence of bleeding events in this study (1.8% to 4.9% for any bleeds, including major, CRNM, and minor). Although it is difficult to compare bleeding risk across studies due to various standards of care, measures of bleeding and patient populations, all bleeding observed in this study appeared to be lower than the incidence of all bleeds reported in other dose-ranging studies for dabigatran (7.2% to 18.1%), rivaroxaban (6.3% to 18.2%), and apixaban (3.3% to 9.9%) (21–23). In this particular study many of the patients were treated in Eastern Europe where long hospital stays and relative immobility post-surgery are considered the standard of care, both of which may have contributed to the low bleeding incidence. Therefore, the relatively low incidence rate did not allow the characterisation of an exposure-response relationship for bleeding.

While the conclusion that edoxaban prevented DVT after hip surgery and dose response was established by Cochran-Armitage with a significance of \( p < 0.001 \) were presented in a previous publication (16), the focus of this current manuscript was the exposure-response relationship of these data, particularly efficacy. This pharmacometric analysis demonstrated a clear relationship between edoxaban exposure and efficacy. In addition, the Bayesian methods provide an integrated approach to the cumulative data for this drug by incorporating informative priors from the previous studies. This pharmacometric analysis nicely complements an earlier publication showing a clear relationship between exposure and safety (24). Well-defined exposure and predictable exposure-response are particularly important attributes for these novel anticoagulants in order to determine the optimum therapeutic concentrations and identify the factors contributing to variability in exposure or response. Vulnerable subgroups, such as patients with renal insufficiency, could be identified and doses optimised to prevent thromboembolic events while reducing the potential for adverse events, notably bleeding.

This study included only once-daily regimens of edoxaban, and these metrics were proportional to dose with no relative differences across the treatments. In a phase II study in patients with AF, both once-daily and twice-daily regimens were administered. For the same total daily dose the twice-daily regimen, with higher trough concentrations, showed a greater incidence of bleeding. The logistic regression analysis of plasma edoxaban exposure and bleeding demonstrated that edoxaban trough concentration was the most robust exposure metric predictor of bleeding (24).

While edoxaban was recently approved in Japan for DVT prevention (25), two other FXa inhibitors, rivaroxaban and apixaban, have also been recently approved or are in development for this in-

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**Figure 2: Relationships between incidence of VTE (top row) and metrics of edoxaban exposure.** Circles and triangles represent observed responses (0 = no event; 100 = event). Diamonds and whiskers represent the observed mean and standard error probability of event calculated at 20% quantities of exposure. These values are also tabulated below the graph. The solid line represents the logistic model prediction and the shaded area represents the 90% confidence interval. \( \Pr(<|t|) < 0.005 \) is the probability that the slope of the relationship differs from 0.
dication. Both rivaroxaban and apixaban are rapidly absorbed with peak concentrations observed in 1 to 4 h (2). Both drugs are eliminated by multiple pathways involving metabolism and renal elimination with terminal elimination half-lives observed as 9 to 13 h and 8 to 15 h for rivaroxaban and apixaban, respectively (2). Apixaban was studied in doses of 5, 10 or 20 mg once daily or 2.5, 5 or 10 mg twice daily compared with enoxaparin or warfarin at standard doses for DVT prevention following orthopedic surgery. No clear dose-response was observed across the six dose regimens for VTE, and there was a dose-related increase in total adjudicated bleeding (23). Since the twice-daily dose regimens showed a trend for greater efficacy compared with once daily dose regimens, the 2.5 mg twice-daily dose was brought forward to phase III clinical studies based on a therapeutic utility index (26). An initial study comparing 2.5 mg twice daily apixaban with 30 mg twice daily enoxaparin (active control) failed to demonstrate the non-inferiority of apixaban (27). However, a second phase III study did demonstrate the non-inferiority of 2.5 mg twice daily apixaban versus 40 mg enoxaparin once daily (28). Rivaroxaban has been recently approved in the US and Europe for DVT prevention. Two Phase II studies were conducted for rivaroxaban in DVT prophylaxis with once- or twice-daily dosing totaling 5 mg to 20 mg daily (21, 29). Pharmacometric analyses showed that the twice-daily and once-daily dose regimens had predictable PK profiles and showed similar safety and efficacy profiles. The 10 mg once-daily dose regimen was selected for phase III clinical study based on the most favourable profile and the lowest potential for exposure to be outside the variability range confidence interval for the typical patient with extreme demographic characteristics (30). This dose regimen has been approved by the US Food and Drug Administration (31) and European Medicines Agency (32) for DVT prevention.

Thus, pharmacometric analyses are important for understanding the relationship of plasma concentrations of edoxaban to bleeding and to efficacy, and in order to identify the impact of various patient factors to drug exposure or to inherent bleeding or thrombotic risk in order to optimise risk/benefit for this anticoagulant. The pharmacometric analyses demonstrated that edoxaban doses up to 90 mg once daily have robust dose-proportional exposure and a well-defined exposure-response relationship of anticoagulant activity, leading to reduced VTE incidence following hip replacement surgery.

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Conflicts of interest
JM, MS, IP, and DES are employees of Daiichi Sankyo. HK and MG are employees of Phar sĩght Corporation and were retained by Daiichi Sankyo to provide scientific consulting services on edoxaban. SR is a former employee of Daiichi Sankyo.

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